FosterHealth

FOSTER HEALTH INC.
21 - 21 Dallas Road
Victoria, British Columbia
Canada, V8V 4Z9
Tel:(250) 381-9133
Fax: (250) 382-9137
E-mail jplafleur@fosterhealth.ca

Via FedEx

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US Department of Commerce
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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia
22313 - 1450
USA

ATTENTION: **Mr. Frank Choi,**
Patent Examiner
Technology Center 1600

Dear Sir,

Re: Patent Application #10/600,028 - 06/23/2003

In further reference to this matter, please note that we are acting on our on behalf so that you have our permission to contact us directly by mail and phone and fax or email.

Please find enclosed the following:

1. "Compositions and Methods for Nutritional Prevention and Treatment of AIDS-Associated conditions." Cross Reference To Related Applications. It seems that you do not yet have this document in your files.

2. "When the nutritional supplements stop: Evidence from a double-blinded, HIV Clinical Trial at Mengo Hospital, Kampala Uganda." *Journal of Orthomolecular Medicine*, Vol. 23, No. 3, 2008.

3. "Successful Orthomolecular Treatment of AIDS: Accumulating evidence from Africa." *Journal of Orthomolecular Medicine*, Vol 21, No. 4, 2006.

4. "A role for the Antioxidant Defense System in Preventing HIV" *Medical Hypotheses* (2007) 69, 1277-1280.

5. "Nutritional Supplements Can Delay the Progression of AIDS in HIV-infected Patients: Results from a Double-Blinded Clinical Trial at Mengo Hospital" *Journal of Orthomolecular Medicine*, Vol. 22, No. 3, 2007.

We believe that these documents address the issues of "obviousness" and "enablement" as well as the issue of 'claimed weight percents', referenced in your Detailed Action.

I trust this is sufficient and we look forward to hearing further from you if you require any further supporting documentation.

Yours truly,

JP Lafleur
VP Business Development
Foster Health Inc.

COMPOSITIONS AND METHODS FOR NUTRITIONAL PREVENTION AND TREATMENT OF AIDS-ASSOCIATED CONDITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of application Serial No. 10/600,028, filed June 23, 2003, which claims benefit of U.S. Provisional Application No. 60/390,509, filed June 24, 2002, both of which are hereby incorporated by reference in their entirety, and to which applications we claim priority.

FIELD OF INVENTION

[0002] The present invention relates to nutraceutical compositions and methods of using the same for preventing and treating immune system deficiencies and other conditions associated with acquired immunodeficiency syndrome (AIDS).

BACKGROUND OF THE INVENTION

[0003] Acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS) is a condition of the human immune system resulting from infection with the human immunodeficiency virus (HIV). Sepkowitz, K.A. (June 2001). "AIDS--the first 20 years". N. Engl. J. Med. 344 (23): 1764–72. The condition progressively reduces the effectiveness of the immune system, leaving individuals susceptible to opportunistic infections and tumors. HIV is a lentivirus member of the retroviral family and exists as two known strains: HIV-1 and HIV-2. HIV-1 is more virulent, more easily transmitted, and the cause of most HIV infections globally. HIV-2 is less transmittable and is found mainly in West Africa. HIV infection is now a pandemic. Kallings, L.O. (2008). "The first postmodern pandemic: 25 years of HIV/AIDS". J Intern Med 263 (3): 218–43. In 2007, an estimated 33.2 million people lived with the disease worldwide, and it killed an estimated 2.1 million people, with over three-quarters of these deaths occurring in sub-Saharan Africa. UNAIDS, WHO (December 2007). "2007 AIDS epidemic update" (PDF) Retrieved on 03/9/2009.

[0004] Despite enormous scientific effort and expense, there is still no vaccine or cure for HIV. Conventional treatments for AIDS and HIV involve, for example, combinations of nucleoside and non-nucleoside analog reverse transcriptase inhibitors and HIV protease inhibitors, which both aim to inhibit viral replication. While these treatments can slow the course of the disease, reducing both mortality and morbidity of HIV infection, these drugs are

expensive and not widely available in all countries, especially in developing countries where HIV/AIDS is prevalent. Palella FJ Jr, *et al* (1998). "Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators". N. Engl. J. Med 338 (13): 853–860. Conventional antiretroviral treatments may also cause adverse side effects. Side effects include, e.g., cardiovascular disease, diabetes, and cancer. One of the most widely used drugs, azidothymidine (AZT), for example, is a carcinogen that can eventually promote cancer. Further, HIV is developing resistance to such antiretroviral agents through accelerated viral evolution. For example, drug resistant strains of HIV-1 have appeared in cities such as New York, Los Angeles and Vancouver.

[0005] In addition to antiretroviral therapies, some investigators have considered nutritional approaches to HIV/AIDS. However, these earlier studies generally focused on supplementing individual nutrients and failed to provide correct combinations addressing the numerous health issues associated with AIDS. For example, it has been demonstrated that daily glutamine supplementation can stabilize the intestinal permeability of AIDS patients, but in this approach many other significant symptoms associated with AIDS remained unaddressed. Noyer, C.M., et al. "A double-blind placebo-controlled pilot study of glutamine therapy for abnormal intestinal permeability in patients with AIDS". Am. J. Gastroenterol, 93(6): 972-975 (1998). Similarly, a mixture of beta-hydroxy beta-methylbutyrate, glutamine and arginine has been shown to reduce lean tissue loss in patients suffering from AIDS-associated wasting, but again that combination failed to address most other AIDS-associated problems. Clark, R.H., et al "Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study." J. Parenter Enteral. Nutr. 24(3): 133-139 (2000). Thus, while various approaches have reduced isolated symptoms of AIDS patients by correcting one or a few nutritional deficiencies, other major deficiencies and their symptoms have not been addressed concomitantly.

[0006] With the pandemic spread of HIV and the lack of inexpensive therapies that address the myriad of afflictions associated with AIDS, there remains a need for effective nutritional approaches. The present invention provides methods, compositions, and kits for use in the prevention and treatment of AIDS and AIDS-related conditions.

SUMMARY OF THE INVENTION

[0007] The present invention addresses the aforementioned problems in the art through the provision of neutraceutical compositions that help correct the enzyme deficiencies created by HIV replication in vivo, and accordingly find use in preventing and/or alleviating the AIDS-associated conditions and the clinical symptoms thereof.

[0008] In one aspect, the invention provides neutraceutical compositions comprising a selenium component, a cysteine component, a glutamine component, and a tryptophan component. In one embodiment, the selenium component and the cysteine component are provided at least in part as selenocysteine. In one embodiment, selenocysteine comprises at least about 30%, preferably at least about 50%, more preferably at least about 70%, and as much as 90-100% of the selenium and cysteine components.

[0009] In some embodiments, the neutraceutical composition comprises from about 100 to about 1000 micrograms of selenium, from about 1 to about 4 grams of cysteine, from about 10 to about 25 grams of glutamine, and from about 1 to about 4 grams of tryptophan.

[0010] In another embodiment, the neutraceutical composition further comprises a vitamin component, wherein said vitamin component comprises one or more of vitamin A, niacin, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin D, vitamin C, vitamin E, vitamin K, biotin, and folic acid.

[0011] In some embodiments, the neutraceutical composition comprises one or more of niacin, B1, B6, C and/or E. In some embodiments, the vitamin component is selected from the group consisting of B1, B6, C and/or E.

[0012] In another embodiment, the neutraceutical composition comprises a second/additional mineral component; wherein said second mineral component comprises one or more of calcium, boron, copper, chromium, manganese, magnesium, zinc, sulfur, molybdenum, vanadium, iodine, iron and strontium.

[0013] In some embodiments, the neutraceutical composition comprises one or more of magnesium, zinc and sulfur. In some embodiments, the second mineral component is selected from the group consisting of magnesium, zinc and sulfur.

[0014] In further embodiments, the neutraceutical composition further comprises one or more of inositol, choline, para-amino benzoic acid and silica.

[0015] In another aspect, methods for correcting enzyme deficiencies in patients in need thereof are provided, comprising administering to said patient a neutraceutical composition as described herein. In one embodiment, the patient has or is suspected of having a viral infection. In one embodiment, the virus is a Human Immunodeficiency Virus (HIV). In another embodiment, the virus is a Hepatitis B or C virus. In another embodiment, the virus is a Coxsackie virus.

[0016] In another aspect, methods are provided for preventing and/or alleviating the clinical symptoms of Acquired Immune Deficiency Syndrome in an HIV+ patient, comprising administering to said patient a neutraceutical composition as described herein.

[0017] In a still further aspect, methods for increasing CD4+ T cells in an HIV+ patient are provided, comprising administering to said patient a neutraceutical composition as described herein.

DETAILED DESCRIPTION

Nutraceutical Compositions

[0018] One aspect of the present invention provides nutraceutical compositions. The nutraceutical compositions provide combinations of nutrients that may be deficient in immuno-compromised and/or virally-infected individuals. The nutraceutical compositions of the present invention find use as nutritional supplements for such individuals and for preventing and/or treating AIDS-associated conditions.

[0019] In some embodiments, the nutraceutical composition comprises selenium and at least one amino acid selected from cysteine, glutamine, and tryptophan. In some preferred embodiments, the nutraceutical composition comprises selenium and all three amino acids cysteine, glutamine and tryptophan.

[0020] As used herein, "nutraceutical composition" refers to any edible material that comprises one or more nutrients in a nutrient combination. "Edible" material includes material in any form that can be ingested and/or in a form that can be converted to an ingestible form, such as, by dissolving in water. For example, the nutraceutical composition can be in the form of

a powder, capsule, or pill, which contains a combination of nutrients described herein. Alternatively, the nutraceutical composition can be any food and/or drink, such as a foodstuff enriched with one or more nutrients disclosed herein or a drink formulated to contain such nutrients.

[0021] "Nutrients" as used herein refers to the components of nutraceutical compositions that serve a biochemical and/or physiological role in the human or animal body. "Nutrients" includes such substances as amino acids (both essential and non-essential), vitamins, minerals and trace elements and mineral, micronutrients, and the like, as well as other bioactive materials, such as components of enzymes or compounds biosynthetically produced by human or animal enzymes. "Nutrients" is used herein interchangeably with related terms such as "nutrient supplements" or "supplements", "nutrient substances" or "substances".

[0022] The individual nutrient components may be provided in any form or combination of forms, preferably in a form allowing adequate or high bioavailability and little or no toxicity. Amino acid components, for example, can be provided as naturally-occurring L-amino acids and, unless otherwise noted, amino acids described herein are assumed to be in the L-conformation. The commercially available nutrient components useful in the practice of the present invention can be used as supplied in pharmaceutically acceptable purity. A reference to a substance includes the essentially pure substance, as well as the substance having the kinds and amounts of impurities as the skilled artisan knows or expects to be present in the commercially available substance.

[0023] Exemplary forms and sources of the components selenium, cysteine, glutamine, and tryptophan are described below. Individual components also can be provided in various amounts and in various relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described below, other forms, sources, amounts and proportions of selenium, cysteine, glutamine and tryptophan useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

Selenium Component

[0024] Selenium is a nonmetal chemical element with the atomic number 34, represented by the chemical symbol Se. Selenium is considered a trace mineral, as the human body normally

only needs small amounts of it to function properly. Nonetheless, selenium is a vital trace element with multiple roles in the growth and functioning of living cells in higher animals and humans. At the molecular level, selenium (as selenocysteine) is an essential component of the active sites of the antioxidant enzyme glutathione peroxidase. It is also needed in at least about fifteen other selenoproteins, such as, for example, the enzymes participating in thyroid functions, such as mammalian thioredoxin reductase and iodothyronine-5'-deiodinase, which converts thyroxine (T4) to triiodothyronine (T3).

[0025] Selenium rarely occurs in its elemental state in nature. It is found in certain foods, through uptake by plants from the soil, in the form of the selenoamino acids, selenomethionine and selenocysteine, as well as their derivatives. As the element is unevenly distributed in the earth's crust, dietary supplements are also available commercially. Organic selenium compounds generally are preferred for supplementation due to their superior bioavailability. For example, a selenium-enriched edible plant part, where the selenium metabolically accumulates in the form of bioavailable organic selenium compounds, can provide this nutrient. Plants that naturally contain higher levels of the sulfur containing amino acids, such as those from the *Allium* and *Brassica* species for example, provide a preferred selenium source. One particular example is selenium-enriched garlic. See, e.g., U.S. Patent No. 7,014,874 to Majeed et al.

[0026] Other sources of selenium from foods include, for example, brazil nuts; mixed nuts; grains, yeast, such as Brewer's yeast (e.g., from LewisLab) or Vegetarian Support yeast (e.g., from Red Star), Red Star NBC600, or Kal flakes; wheat germ, preferably raw wheat germ, wheat bran, preferably raw wheat bran, wheat, preferably durum grain wheat or matzo whole wheat or hard red spring/winter wheat, whole wheat spaghetti or pasta, enriched spaghetti or pasta, macaroni, puffed wheat, preferably enriched puffed wheat or sweet puffs (e.g., from Quaker), and whole wheat flour; whelk; semolina; mustard seed, preferably yellow mustard seed; as well as fish and shellfish, such as swordfish, cuttlefish or cod, preferably Atlantic cod, or tuna, preferably white, more preferably light tuna canned in oil, or more preferably canned in water, anchovy, such as canned anchovies, and oysters, preferably Pacific oysters or Eastern farmed oysters, mussels, preferably blue mussels, and clams; red meat; chicken, including chicken skin; turkey, including turkey giblets and turkey skin; liver, e.g., lamb, chicken, turkey, pork or calf liver; kidney, e.g., beef, lamb, veal or pork kidney; spleen, such as veal spleen; thymus, e.g., veal thymus; gizzard, e.g., chicken or turkey gizzard; spleen, e.g., beef spleen; pancreas, e.g., lamb or

preferably pork pancreas; octopus; caviar, including black or red caviar; mushrooms, preferably shiitake dried mushrooms; sunflower seed kernels; spinach spaghetti or spinach pasta; and eggs, including egg noodle pasta. Also selenium in an organically chelated form can be obtained from Dews Research Laboratory, FM 1821 North, Mineral Wells, Tex. 76067. See also, e.g., U.S. Patent No. 6,585,998 to Cartwright, et al. Additional sources of selenium can be found in, for example, Hatfield, D.L., Berry, M.J., and Gladyshev V.N. (editors) "Selenium. Its Molecular Biology and Role in Human Health (2^{nd} edition)". New York: Springer Science + Business Media, 2006.

[0027] In some embodiments, nutraceutical compositions of the instant disclosure provide selenium as L-selenomethionine or L-selenocysteine or a combination of both. The selenocysteine form, albeit an unusual amino acid, is preferred in some embodiments. In some preferred embodiments, selenocysteine comprises at least about 30%, at least about 50%, at least about 70%, at least about 80%, at least about 90%, or as much as about 100% of the selenium component provided.

[0028] In some embodiments, the nutraceutical composition comprises selenium in an amount from about 0.0004 to about 0.0008 weight percent. In some embodiments, the nutraceutical composition comprises from at least about 0.0005, at least about 0.0006, or at least about 0.0007 weight percent of selenium. In some embodiments, the nutraceutical composition comprises less than about 0.0007, less than about 0.0006, or less than about 0.0005 weight percent of selenium.

[0029] In some embodiments, the nutraceutical composition comprises from about 100 to about 1,000 micrograms of selenium. In some embodiments, the composition comprises from at least about 200, at least about 300, at least about 500, or at least about 700 micrograms of selenium. In some embodiments, the composition comprises less than about 400, less than about 500, less than about 700, less than about 800, or less than about 900 micrograms of selenium.

Cysteine Component

[0030] Cysteine (abbreviated as Cys or C) is an α-amino acid with the chemical formula $HO_2CCH(NH_2)CH_2SH$. Having a polar thiol side chain, cysteine is classified as a hydrophilic amino acid. Ordinarily synthesized by the human body, it is considered a non-essential amino acid. Cysteine can be found in most high-protein foods, including, animal sources such as, for

example, pork, sausage meat, chicken, turkey, duck, luncheon meat, eggs, milk, whey protein, ricotta, cottage cheese, and yogurt; as well as plant sources such as, for example, red peppers, garlic, onions, broccoli, Brussels sprouts, oats, granola, and wheat germ.

[0031] Food-grade L-cysteine also may be purified cheaply in high yield by hydrolysis of human hair or other sources, such as feathers and pig bristles. L-cysteine has also recently become accessible via fermentation using sources of non-human and non-animal origin, e.g., as commercially available from Wacker Chemie AG. Another potential source is bacteria. In some bacteria, serine is converted to O-acetylserine by the enzyme serine transacetylase, and then to cysteine by the enzyme O-acetylserine (thiol)-lyase, which uses sulfide sources. See, e.g., Hell, R. 1997. "Molecular physiology of plant sulfur metabolism" Planta 202:138-148.

[0032] In some embodiments, nutraceutical compositions of the instant disclosure provide cysteine as N-acetyl cysteine or L-selenocysteine or a combination of both. The selenocysteine form, albeit an unusual amino acid, is preferred in some embodiments. In some preferred embodiments, selenocysteine comprises at least about 30%, at least about 50%, at least about 70%, at least about 80%, at least about 90%, or as much as about 100% of the cysteine component provided.

[0033] In some embodiments, the nutraceutical composition comprises cysteine in an amount from about 3.4 to about 37.5 weight percent. In some embodiments, the nutraceutical composition comprises from at least about 4, at least about 10, at least about 20, or at least about 30 weight percent of cysteine. In some embodiments, the nutraceutical composition comprises less than about 10, less than about 20, less than about 30, or less than about 35 weight percent of cysteine.

[0034] In some embodiments, the nutraceutical composition comprises from about 1 to about 4 grams of cysteine, in the form of N-acetly-cysteine or L-selenocysteine. In some embodiments, the composition comprises from at least about 1.5, at least about 2, at least about 3, or at least about 3.5 grams of N-acetly-cysteine or selenocysteine. In some embodiments, the composition comprises less than about 2, less than about 2.5, less than about 3, or less than about 3.5 grams of N-acetly-cysteine or selenocysteine.

Glutamine Component

[0035] Glutamine (abbreviated as Gln or Q) is an α-amino acid with the chemical formula $HO_2CCH(NH_2)CH_2CH_2CONH_2$. It is synthesized by the human body from the amino acid glutamic acid or glutamate, where the hydroxyl side chain of glutamic acid is replaced by an amide. Its polar amide side chain makes glutamine another hydrophilic amino acid. Glutamine is considered a conditionally essential amino acid because under certain circumstances the human body is unable to produce enough glutamine to meet its needs, making it "essential" during these times to obtain glutamine from the diet.

[0036] Dietary sources of L-glutamine include most high-protein foods, for example, beef, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley. Small amounts of free L-glutamine are also found in vegetable juices and fermented foods, such as miso. As a dietary supplement, glutamine is commercially available in protein powders and powdered drink mixes. E.g., The Vitamin Shoppe, 1430 Van Ness Ave, San Francisco, CA 94109.

[0037] Preferred food sources of glutamate, a related amino acid from which glutamine can be derived, include, for example, gluten; soy, e.g., from Protein Tech, and including soy flour or soy meal; cottonseed flour or meal; sunflower seed kernels; sesame flour; peanut flour; cheese, such as Port du Salut, cheddar, Tilsit, brick, lagerkaese, Muenster, goat, Cheshire or Swiss, preferably Colby, Gruyere, or Monterey, more preferably cheddar, Gouda, Edam, caraway, provolone, or mozzarella, more preferably Romano, and most preferably parmesan cheese; cod, preferably Atlantic cod; yeast, such as Red Star NBC600, Vegetarian Support yeast from Red Star and Kal flakes; gelatin; lupin; meat extender; spirulina, e.g., dried spirulina or sea veg spirulina; tofu; koyadofu; safflower seed meal; soybeans; beans; pork skins; milk powder, preferably nonfat milk powder; whelk; butternuts; peanuts, such as Virginia peanuts, preferably Valencia peanuts, more preferably Spanish peanuts; peanut butter; squash seeds; pumpkin seeds; flax seeds; watermelon seeds; yeast; almonds; rabbit, preferably wild rabbit; walnuts, preferably black walnuts; and breadnut seeds.

[0038] In some embodiments, nutraceutical compositions of the instant disclosure provide glutamine as L-glutamine.

[0039] In some embodiments, the nutraceutical composition comprises glutamine in an amount from about 55.0 to about 86.0 weight percent. In some embodiments, the nutraceutical

composition comprises from at least about 60.0, at least about 70.0, at least about 80.0, or at least about 85.0 weight percent of glutamine. In some embodiments, the nutraceutical composition comprises less than about 60.0, less than about 70.0, less than about 80.0, or less than about 85.0 weight percent of glutamine.

[0040] In some embodiments, the nutraceutical composition comprises from about 10 to about 25 grams of glutamine. In some embodiments, the composition comprises from at least about 12, at least about 15, at least about 20, or at least about 23 grams of glutamine. In some embodiments, the composition comprises less than about 15, less than about 18, less than about 20, or less than about 23 grams of glutamine.

Tryptophan Component

[0041] Tryptophan (abbreviated as Trp or W) is an α-amino acid with the chemical formula $C_{11}H_{12}N_2O_2$. The distinguishing structural characteristic of tryptophan is its indole functional group. This bulky aromatic side chain makes it a hydrophobic amino acid. While only the L-stereoisomer of tryptophan is used in structural or enzyme proteins, the D-stereoisomer is occasionally also found in naturally-produced peptides. Pallaghy, P.K. et al (1999). "Solution structure of contryphan-R, a naturally-occurring disulfide-bridged octapeptide containing D-tryptophan: comparison with protein loops". Biochemistry 38 (35): 11553–9. As the human body cannot synthesize tryptophan, it is considered an essential amino acid in the human diet.

[0042] Plants and microorganisms, however, commonly synthesize tryptophan, for example, from shikimic acid or anthranilate. Radwanski, E.R., et al. (1995). "Tryptophan biosynthesis and metabolism: biochemical and molecular genetics". Plant Cell 7 (7): 921–34. Tryptophan is also produced industrially via the fermentation of serine and indole using either wild-type or genetically modified *E. coli*, where conversion is catalyzed by the enzyme tryptophan synthase. See, e.g., Ikeda, M. (2002). "Amino acid production processes". Adv. Biochem. Eng. Biotechnol. 79: 1–35.

[0043] Tryptophan is a constituent of most protein-based foods and dietary proteins. It is particularly plentiful, for example, in chocolate, oats, bananas, durians, mangoes, dried dates, milk, yogurt, cottage cheese, red meat, eggs, fish, poultry, sesame, chickpeas, sunflower seeds, pumpkin seeds, spirulina, and peanuts. Several high-quality sources of L-tryptophan are also available in the form of dietary supplements, for example, in health food stores and pharmacies.

Tryptophan is also sold as a prescription drug (Tryptan), prescribed, e.g., by psychiatrists to augment antidepressant drugs. Various metabolites of tryptophan are also known, including, for example, 5-hydroxytryptophan or hydroxytryptophan L-S (5-HTP), which is marketed in Europe for depression and other indications under the brand names Cincofarm and Tript-OH.

[0044] Preferred food sources of tryptophan include, for example, soy, such as from Protein Tech, and including soy flour or soy meal; sesame flour; yeast, such as Kal flakes, Vegetarian Support Yeast, e.g., form Red Star, more preferably Red Star NBC600, and most preferably Brewers' Yeast, e.g., from LewisLab; spirulina, preferably dried spirulina or sea veg spirulina; gluten; beans, preferably winged beans; soybeans; cottonseed flour or meal; tofu; koyadofu; sunflower seed kernels; cod, preferably Atlantic cod; fish roe; whelk; squash seeds; pumpkin seeds; meat extender; cheese, such as mozzarella or Swiss, preferably Gruyere or Romano cheese, most preferably parmesan cheese; squash seeds; pumpkin seeds; elk, preferably lean elk; mustard seeds, preferably yellow mustard seeds; milk powder, preferably nonfat milk powder; peanut flour; cottonseeds; sesame seeds or sesame butter or meal; flax seeds; caribou, preferably lean caribou; rabbit, preferably wild rabbit; goose, preferably domesticated goose; duck, preferably domestic duck; goat, preferably lean goat; safflower seed meal; wheat germ; tahini, e.g., from roasted kernels, preferably from raw kernels; fenugreek seed; watermelon seeds; chicken; beef liver; pork, such as pork loin, pork chops or pork leg, preferably lean pork, more preferably pork pancreas; boar, preferably lean bore; and ham, preferably fresh, lean ham.

[0045] Tryptophan is involved in glutathione peroxidase production and is also needed in the biosynthesis of niacin and serotonin. Brown, R.R., et al "Implications of interferon-induced tryptophan catabolism in cancer, auto-immune diseases and AIDS". Adv. Exp. Med. Biol. 294: 425-435 (1991). Tryptophan is believed also to play a role in defense against infection, so that deficiency results in immune incompetence. Without being bound to any particular hypothesis or theory, it is believed that when infection occurs, the body induces tryptophan-catabolizing enzymes to starve invading pathogens of this nutrient, which in turn further decreases its availability for the body's own needs. Fawkes, S.W. "Tryptophan metabolism in chronic disease and AIDS". Forefront - Health Investigations. July 1992.

[0046] In some embodiments, nutraceutical compositions of the instant disclosure provide tryptophan as hydroxytryptophan, including 5-HTP.

[0047] In some embodiments, the nutraceutical composition comprises tryptophan in an amount from about 3.4 to about 37.5 weight percent. In some embodiments, the nutraceutical composition comprises from at least about 4, at least about 10, at least about 20, or at least about 30 weight percent of tryptophan. In some embodiments, the nutraceutical composition comprises less than about 10, less than about 20, less than about 30, or less than about 35 weight percent of tryptophan.

[0048] In some embodiments, the nutraceutical composition comprises from about 1 to about 4 grams of tryptophan. In some embodiments, the nutraceutical composition comprises from at least about 1.5, at least about 2, at least about 3, or at least about 3.5 grams of tryptophan. In some embodiments, the nutraceutical composition comprises less than about 2, less than about 2.5, less than about 3, or less than about 3.5 grams of tryptophan.

[0049] In some preferred embodiments, the amino acids cysteine, glutamine and tryptophan are provided together in the forms of N-acetyl cysteine or L-selenocysteine, L-glutamine, and 5-HTP, respectively, along with selenium, preferably also in the form of L-selenocysteine. It is particularly preferable to provide at least some of selenium and cysteine together in the form of selenocysteine. In some preferred embodiments, selenocysteine comprises at least about 20%, at least about 30%, at least about 50%, at least about 70%, at least about 80%, at least about 90%, or as much as about 100% of the total selenium plus cysteine components provided.

[0050] Without being bound to any particular theory or hypothesis, it is believed that replication of HIV in its host depletes nutrients from the host body. In particular, HIV-1 encodes a homologue of the human selenoenzyme glutathione peroxidase. Tylor, E.W. et al., "HIV-1 encodes a sequence overlapping env gp41 with highly significant similarity to selenium-dependent glutathione peroxidases". J. AIDS and Human Retrovirology. 15: 393-394 (1997). This requires the replicating virus to deprive seropositive individuals of this selenoenzyme, as well as its four main components: selenium, cysteine, tryptophan, and glutamine, which are thus removed from the host body. Maiorino, K.D., "Probing the presumed catalytic triad of a selenium-containing peroxidase by mutational analysis". Z. Ernahrungswiss. 37 Suppl. 1: 118-121 (1988). Such depletion may eventually cause severe deficiencies in these and other substances, which in turn may lead to the conditions and symptoms commonly associated with AIDS. This would explain, for example, why AIDS symptoms are so diverse and why so many

different organs are adversely affected, even when showing little evidence of direct HIV-1 impact.

[0051] The present invention provides nutritional approaches to preventing and/or treating AIDS-associated conditions by supplementing two or more of these nutrients, as well as, optionally, other nutrient substances depleted by viral replication, such as glutathione peroxidase and/or other components of this enzyme. Additional substances also can be provided in various forms, amounts and/or relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described, other forms, sources, amounts and proportions useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

[0052] In some embodiments, the nutraceutical composition further includes glutathione and/or glutathione peroxidase. Glutathione is a peptide of three amino acids, glycine, glutamic acid and cysteine (γ-L-glutamyl-L-cysteinylglycine). Glutathione is known to act as a nucleophilic scavenger in the body, and as an antioxidant in the event of tissue injury. It thus plays a major role as a protector of biological structures and functions. Glutathione useful in the present invention can be obtained from, for example, Glen Madison Co., 38306 Pine Creek Place, Murrieta, Calif. 92562.

[0053] In some embodiments, the nutraceutical composition further includes niacin and/or serotonin.

[0054] In some embodiments, the nutraceutical composition further includes alpha lipoic acid and/or ascorbic acid.

[0055] In some embodiments, the nutraceutical composition further includes one or more additional vitamins and/or minerals. In some embodiments, the nutraceutical composition further includes one or more of the vitamins B1, B6, C, and/or E. In some embodiments, one or more of the minerals magnesium and/or zinc are included. Again without being bound to any particular theory or hypothesis, the vitamins B1, B6, C and E and the minerals magnesium and zinc act as cofactors in the body's utilization of the four nutrients selenium, cysteine, glutamine and tryptophan, which are believed to be depleted during HIV replication in the host body.

[0056] In some preferred embodiments, the nutraceutical composition includes vitamins B1 and C. In some preferred embodiments, the nutraceutical composition includes vitamins C and E. In some preferred embodiments, vitamins B1 and C are included together with niacin. In some embodiments, the nutraceutical composition comprises about 1.9 milligrams of vitamin B1. In some embodiments, the nutraceutical composition comprises about 1.9 milligrams of vitamin B6.

[0057] In some embodiments, vitamin C is provided in the form of calcium ascorbate. In some preferred embodiments, the nutraceutical composition comprises about 23 milligrams of vitamin C, preferably as calcium ascorbate.

[0058] In some embodiments, vitamin E is provided in the form of d-alpha-tocopheryl succinate. Consistent with the recommendations of the I.U.P.A.C.--I.U.B. Joint Commission on Biochemical Nomenclature, the term vitamin E is used herein to describe all tocol and tocotrienol derivatives, including esters, exhibiting qualitatively the biological activity of alpha-tocopherol. Where a specific amount or portion of vitamin E is mentioned, it is understood that it pertains to that amount of d-alpha-tocopherol and any amount of any other biologically active tocol or tocotrienol species that is equivalent, in terms of international units, to the specific amount of d-alpha-tocopherol mentioned. Vitamin E suitable for use in the present invention is available from, for example, Hoffman-La Roche Inc., 45 Waterview Blvd., Parsippany, N.J. 07054. In some preferred embodiments, the nutraceutical composition comprises about 5 IU of vitamin E, preferably as d-alpha-tocopheryl succinate.

[0059] In some embodiments, the nutraceutical composition comprises about 23 micrograms of magnesium. In some embodiments, the nutraceutical composition comprises about 1.1 micrograms of zinc.

[0060] As with the nutrient supplements discussed above, the additional vitamins and/or minerals may be provided in any form, preferably in a form allowing adequate or high bioavailability and no or low toxicity. The additional vitamins and/or minerals may also be provided in various amounts and relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described, other forms, sources, amounts and proportions of vitamins and minerals useful in the present invention

would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

[0061] In some embodiments, the nutraceutical composition further includes one or more of the 24 nutrients listed in Table 1 below. In some embodiments, the nutraceutical composition comprises the amounts suggested in the Table, for the corresponding nutrient component.

Table 1.

Additional Nutrient Supplements	**Suggested amounts**
Calcium	23 mg
Boron	0.2mg
Vanadium	2 mcg
Copper	100 mcg
Chromium	8 mcg
Manganese	620 mcg
Silica	770 mcg
AEP Iron (2-amino ethanol phosphate)	600 mcg
Iodine	2.9 mcg
Strontium	25.7 mcg
Molybdenum	0.3 mcg
Vitamin A	390 IU
Provitamin A	390 IU
Vitamin D_3	31 IU
Vitamin B_2	1.9 mg
Vitamin B_3	7.8 mg
D-Calcium Pantothenate	7.8 mg
Vitamin B_{12}	8 mcg
Vitamin K (Phytonadione)	23 mcg
Biotin	8 mcg
Folic Acid	31 mcg
Choline	4 mg
Inositol	4 mg
P.A.B.A. (Para Amino Benzoic Acid)	2 mg

[0062] As with the nutrient supplements discussed above, these additional nutrients may be provided in any form, preferably in a form allowing adequate or high bioavailability and no or low toxicity. The additional supplements may also be provided in various amounts and relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to

the exemplary embodiments explicitly described, other forms, sources, amounts and proportions of these 24 additional nutrient supplements useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

Prevention and Treatment of AIDS

[0063] Another aspect of the present invention provides methods of using the nutraceutical compositions disclosed herein in the prevention and treatment of AIDS-associated conditions. The term "AIDS-associated conditions" is used herein interchangeably with "AIDS" and "AIDS-related conditions", and refers to the symptoms and/or conditions commonly seen in HIV/AIDS patients, and thus conventionally associated with AIDS. These can include, for example, immune system collapse; increased susceptibility to cancer; increased susceptibility to myocardial infarction; muscle wasting; depression; diarrhea; psychosis; dementia, and the like. The declining efficacy of the immune system also leads to opportunistic infections by other pathogens, such as, for example, the bacteria responsible for tuberculosis, which become responsible for their own particular symptoms. Such symptoms and conditions arising from opportunistic infections are also included as conditions associated with AIDS.

[0064] AIDS-associated conditions that may be treated and/or prevented according to the instant invention also include conditions and/or symptoms arising from deficiencies in one or more of the substances needed to produce the selenoenzyme glutathione peroxidase, or arising from a deficiency in the enzyme itself. Again without being bound to any particular theory or hypothesis, it is believed that HIV competes with the infected individual for resources needed to produce glutathione peroxidase, so that these required substances, along with glutathione peroxidase itself, become deficient as the virus replicates. These symptoms and/or conditions include, for example, those associated with deficiencies in selenium, cysteine, glutamine, and/or tryptophan, as well as with deficiencies in glutathione and/or glutathione peroxidase.

[0065] Selenium deficiency has been linked to decreased production of CD4+ T lymphocytes, decreased immunity to disease; as well as to greater susceptibility to myocardial infarction and a prevalence of various forms of cancers, such as cancers of the lung, colon, etc., and Kaposi's sarcoma (with HHV-8). Kiremidijian-Schumacher, L. et al, "Selenium and immune function". Z. Ernahrungswiss. 37 Suppl. 1:50-56 (1998); Wang, R.D. et al,

"Investigation of the effect of selenium on T lymphocyte proliferation and its mechanisms". J. Tongji Med. Univ. 12(1): 33-38 (1992). Symptoms of selenium deficiency can also include low glutathione peroxidase, oxidative stress, depression, and decreased triiodothyronine (hypothyroidism or low T3 syndrome), as well as other symptoms arising from thyroid malfunction. Depressed selenium and impaired lymphocyte production can also lead to opportunistic pathogen infections, which further decrease serum selenium and present their own particular symptoms. Foster, H.D., Aids and the "Selenium-CD4 T Tailspin" the geography of a pandemic. Townsend Letter for Doctors and Patients 209: 94-99 (2000); Sammalkorpi, K., et al. "Serum selenium in acute infections". Infection 16(4): 222-224 (1988). Such symptoms are also considered AIDS-associated conditions that may be treated and/or prevented according to the present invention.

[0066] Cysteine deficiency is known to encourage psoriasis, poor wound and skin healing, abnormal immune function, and secondary infections and cancers. Symptoms of cysteine deficiency also include depressed glutathione and sulfur levels. Any of these symptoms and/or conditions are also considered AIDS-associated conditions that may be treated and/or prevented according to the present invention.

[0067] Glutamine deficiency results in depression, abnormal intestine permeability and associated digestive malfunction, such as diarrhea. Glutamine is important for rapidly dividing cells, e.g., for intestinal cell proliferation in the digestive tract. It also plays a role in intestinal fluid/electrolyte adsorption, as well as mitogenic response to growth factors. Inadequate glutamine is also associated with apoptosis and muscle wasting. Any of these symptoms and/or conditions are also considered AIDS-associated conditions that may be treated and/or prevented according to the present invention.

[0068] Symptoms of inadequate tryptophan include dementia and polyneuropathy, diarrhea, dermatitis and other symptoms of pellagra, depressed niacin and serotonin levels, as well as cognitive deficits and neuroendocrine disregulation, which are particularly seen in the case of prolonged tryptophan deficiency. Any of these symptoms and/or conditions are also considered AIDS-associated conditions that may be treated and/or prevented according to the present invention.

[0069] Glutathione deficiency is associated with impaired T cell function, as well as symptoms seen in paracetamol intoxication. Parker, D., et al, "Safety of late acetylcysteine treatment in paracetamol poisoning". Hum. Exp. Toxicol. 9(1): 25-27 (1990). Symptoms of low glutathione also include general impaired immune function, as intracellular glutathione plays a role in how well T- and B-lymphocytes function, and its availability affects production of macrophages, monocytes, and neutrophils. Low glutathione levels in HIV-1 seropositive patients is associated also with more secondary infections and cancers, and a higher mortality rate. Lee, J. "Amino acid supplement may help people with HIV". News from the Agricultural Research Service. Press release, September 21, 1998. Any of these symptoms and/or conditions are also considered AIDS-associated conditions that may be treated and/or prevented according to the present invention.

[0070] AIDS-associated conditions also refer to conditions and/or symptoms arising from infection with other glutathione peroxidase-encoding viruses, which may lead to a disease progression resembling that seen in HIV infected individuals. Such virus include, for example, Hepatitis B and Hepatitis C viruses, as well as Coxsackie B. Conditions and/or symptoms caused by other human or animal viruses found to encode for glutathione peroxidase, or other selenoenzyme(s), are also considered AIDS-associated conditions.

[0071] "HIV infected individuals", "HIV infection" and related terms as used herein, refer to infection with either (or both) HIV-1 or HIV-2 strains of the virus, unless otherwise specified.

[0072] The present invention provides methods, nutraceutical compositions, and kits for treating and/or preventing AIDS-associated conditions in animal subjects. The term "animal subject" as used herein includes humans as well as other mammals. Non-human applications include, e.g., Colony Collapse Disorder in honey bees and viral conditions in livestock such as pigs, goats, cattle, horses, and chickens, e.g., where such conditions arise from infection with a glutathione peroxidase-encoding virus.

[0073] The term "treating and/or preventing" as used herein includes achieving a therapeutic benefit and/or a prophylactic benefit, respectively. By therapeutic benefit is meant the reversal or amelioration of the underlying disorder being treated. For example, in an AIDS patient, therapeutic benefit includes eradicating or ameliorating one or more of the myriad of conditions and symptoms associated with AIDS, such that an improvement is observed in the patient,

notwithstanding the fact that the patient may still be afflicted with the underlying disorder. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more conditions and/or symptoms arising from infection by opportunistic pathogens. For example, with respect to AIDS, treatment can provide a therapeutic benefit not only when immune function improves, but also when an improvement is observed in the patient with respect to symptoms that accompany opportunistic infections like tuberculosis, such as persistent coughing, pain in the chest, chills, fever and night sweats. Therapeutic benefits also include, e.g., less frequent opportunistic infections, slower disease progression, and/or reduced mortality.

[0074] Therapeutic benefits also include returning to normal body levels of one or more of selenium, cysteine, glutamine, and tryptophan. Again without being bound to any particular theory or hypothesis, it is believed that supplying these nutrients, along with one or more additional nutrient supplements, will address deficiencies caused by loss of certain nutrients upon viral replication. The supplied nutrients can replace this loss and allow biosynthesis of, e.g., glutathione, glutathione peroxidate and/or as precursors for other biochemical substances.

[0075] For prophylactic benefit, a neutraceutical composition of the present invention may be administered to a patient at risk of developing AIDS, in particular, for example, an HIV-infected individual who has not yet developed the major symptoms of AIDS. A nutraceutical composition of the instant invention may also be administered to a patient reporting one or more of the symptoms or conditions commonly associated with AIDS, even though a diagnosis may not yet have been made. In some embodiments, prophylactic treatment may begin even prior to HIV infection, e.g., in patients at high risk for contracting the virus.

[0076] The instant invention also facilitates approaches to treating and/or preventing AIDS-related conditions that generally cause no or few adverse side effects, including fewer adverse side effects than conventionally-used antiretroviral therapies. Also, the nutraceuticals described herein are not known to increase drug-resistance in HIV-1 or HIV-2, nor in other viral or bacterial strains.

[0077] The present invention provides nutraceutical compositions comprising a combination of selenium, with cysteine, glutamine and/or tryptophan, as well as optionally one or more additional nutrients, that can be administered to a patient in need thereof. In preferred embodiments, the nutracetical compositions of the present invention produce a benefit, including

either a prophylactic benefit, a therapeutic benefit, or both, in preventing and/or treating one or more AIDS-associated conditions. Again without being bound to any particular theory or hypothesis, it is believed that AIDS results from deficiencies in selenium, cysteine, glutamine and tryptophan. In some preferred embodiments, the instant invention addresses these deficiencies together, e.g., by providing correct combinations of nutrients. Addressing several important deficiencies together, rather than individually, can provide compelling, superior and/or synergistic benefits.

[0078] For example, in some preferred embodiments, administration of a nutracetucial composition of the instant invention prevents or delays the development of one or more AIDS-associated conditions; and/or reduces its severity and/or duration. In especially preferred embodiments, the progression to AIDS of HIV-infected patients is prevented. In most preferred embodiments, an HIV-infected patient never develops AIDS, e.g., by receiving a nutraceutical composition of the instant invention on an ongoing basis, as described in more detail below.

[0079] In some preferred embodiments, administration of a nutraceutical composition of the instant invention slows, halts and/or reverses one or more AIDS-associated conditions. In some preferred embodiments, administration allows those infected by HIV-1 and/or HIV-2 to live a longer life than if not receiving the nutraceutical composition, including living a life of normal duration; and/or to engage in more normal physical activity than if not receiving the nutraceutical composition, including engaging in normal physical activity. See, e.g., the clinical study results descried in the Examples below. The marked improvements reported there for HIV seropositive individuals, not receiving any antiretroviral therapy, indicates the importance of providing correct combinations of nutrients concomitantly in treating the diverse symptoms and conditions associated with AIDS.

[0080] In some preferred embodiments, administration of a nutraceutical composition of the instant invention results in a statistically significant increase in CD4+ T cell counts, and/or a statistically significant increase in serum glutathione peroxidase levels. CD4+ T cell counts are indicative of an improving immune system; glutathione peroxidase levels normally decline as HIV/AIDS progresses. In some preferred embodiments, administration of a nutraceutical composition of the instant invention causes a statistically significant increase in weight gain, and/or a statistically significant increase in quality of life. e.g., as measured by Karnofsky scores.

See, e.g., The Measurement Group.com. Definition: Karnofsky Severity Rating. http://www.themeasure- mentgroup.com/Definitions/ Karnofsky.html. The statistical significance observed, in any of these measures or parameters, can occur over the course of treatment, preferably within about 5 years, about 2 years, about 1 year, or within about the first 6 months of treatment. See, e.g., the clinical study results descried in the Examples below. The marked improvements reported there within just 1 year for HIV seropositive individuals, not receiving any antiretroviral therapy, again indicates the importance of providing correct combinations of nutrients in treating the diverse symptoms and conditions associated with AIDS.

Administration and Dosage

[0081] The nutraceutical compositions useful in the present invention can be delivered to a patient in need thereof using a number of routes or modes of administration. Nutraceutical compositions for use in accordance with the present invention may be formulated in any conventional manner, e.g., using one or more physiologically acceptable carriers, including excipients and/or auxiliaries, which facilitate processing of the nutrient components into preparations to be delivered to patients. Proper formulation is dependent upon the route of administration chosen.

[0082] In some embodiments, the nutraceutical composition is provided as an adjunct to other treatments, such as in addition to one or more conventional anti-retroviral therapies. In other embodiments, the nutraceutical composition is provided to a patient not receiving any other treatment for HIV/AIDS, e.g., not receiving anti-retroviral treatment. As the nutraceutical compositions of the instant disclosure are relatively inexpensive, they can be made more widely available than anti-retroviral treatments, and be used to treat populations lacking access to more expensive therapies.

[0083] In some embodiments, the nutraceutical composition may be administered in combination with one or more other therapeutic agents. The choice of therapeutic agent that can be co-administered with a composition of the invention will depend, for example, on the degree of disease progression, and the presence of other opportunistic infections, as well as the availability of other treatments, as noted above. In some embodiments, the nutraceutical compositions can be co-administered with one or more anti-retroviral agents, including, for example, (1) nucleoside and nucleotide reverse transcriptase inhibitors (nRTIs), such as, for

example: zidovudine (AZT, ZDV, or azidothymidine), didanosine (ddI), and tenofovir (tenofovir disoproxil fumarate); (2) non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as, for example, efavirenz, nevirapine, delavirdine, and etravirine; (3) protease inhibitors (PIs), such as, for example, saquinavir, ritonavir, and indinavir; (4) integrase inhibitors, such as, for example, raltegravir; (5) early inhibitors or fusion inhibitors, such as, for example, maraviroc and enfuvirtide; (6) maturation inhibitors, such as, for example, bevirimat and Vivecon; and the like.

[0084] Administration of the nutraceutical compositions of the instant invention can begin at various points along disease progression, and can follow a variety of dosing schedules. For example, nutraceutical compositions of the instant invention can be administered to an HIV-infected patient before and/or after symptoms associated with AIDS have developed. For example, in some embodiments, treatment begins just after an individual has tested seropositive for HIV; or during the initial phases of HIV-1 infection when symptoms, if any, are relatively minor. As major symptoms associated with AIDS may take several years to develop in HIV-1 positive individuals, treatment may begin at any point during that time, but in more preferred embodiments, treatment begins soon after viral infection.

[0085] Nutraceutical compositions suitable for use in the present invention include compositions wherein the active nutrient components are present in an effective amount, i.e., in an amount sufficient to produce a therapeutic and/or a prophylactic benefit in at least one AIDS-associated condition being treated. The actual amount effective for a particular application will depend on a number of factors, including, e.g., the severity of symptoms and the route of administration. In preferred embodiments, individual nutrient components are present in the nutraceutical composition in effective proportions relative to one another. Effective proportion refers to the effective amount of a given nutrient component relative to the amounts of one or more other nutrient(s) in combination with it in the nutraceutical composition. Determination of an effective amount and/or effective proportion is within the capabilities of those skilled in the art, based on the teachings provided herein. A person of ordinary skill using techniques known in the art can determine the effective amount and/or effective proportion of the nutrient components used together in the nutraceutical compositions. For example, the dosages used in the clinical trials, set forth in the Examples below, provide guidance to enable one of ordinary skill in the art to select effective dosages of the corresponding nutrient supplements.

[0086] A person of ordinary skill in the art can determine efficacy, for example, by evaluating a number of quantifiable parameters, such as, for example, the parameters used in the clinical trials illustrated in the Examples below. Other techniques would be apparent to one of ordinary skill in the art. A person of ordinary skill in the art would also be able to monitor in a patient the effect of a nutraceutical composition of the present invention, e.g., by monitoring one or more such parameters over time.

[0087] For example, effective amounts and/or proportions may be determined and/or monitored by measuring body levels of one or more of glutathione, glutathione peroxidase, selenium, cysteine, tryptophan, and glutamine. Normalization or a trend towards normal body levels of one or more of these substances can indicate efficacy. Techniques for determining levels of these substances in humans and animal models are known in the art. For example, Gil, et al. measured the glutathione peroxidase levels in blood taken from HIV/AIDS patients and healthy controls. [CITE] Measurement of blood glutathione levels has been discussed, e.g., in Herzenberg, L.A., et al. "Glutathione deficiency is associated with impaired survival in HIV disease". Proc. Nat. Acad. Sci. 94(5): 1967-1972 (1997). Effective dosage can also be determined and/or monitored by measurement of CD4 cell counts and/or serum glutathione peroxidase, as detailed in the Examples below.

[0088] Measuring levels of plasma selenium of adults and serum selenium levels in children also has been described. See, e.g., Baum, M.K., et al, "High risk of HIV-related mortality is associated with selenium deficiency". J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 15(5): 370-374 (1997); Campa, A., et al, "Mortality risk in selenium deficient HIV-positive children". J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 20(5): 508-513 (1999). Measurement of plasma cysteine concentrations has been described, e.g., in Droge, W. "Cysteine and glutathione deficiency in AIDS patients: a rationale for the treatment with N-acetyl-cystein". Pharmacology 46(2): 61-65 (1993); and Breitkreutz, R., et al. "Improvement of immune functions in HIV infection by sulfur supplementation: two randomized trials". J. Mol. Med. 78(1): 55-62 (2000). Werner et al. measured and compared tryptophan levels in serum and cerebrospinal fluids of HIV-infected patients and those of gender and age matched controls. Werner, E.R., et al "Tryptophan degradation in patients infected by human immunodeficiency virus". Biol. Chem. Hoppe Seyler 369(5): 337-340 (1988). See also, e.g., Fuchs, D., et al "Increase of tryptophan in

serum and in cerebrospinal fluid of patient with HIV infection during zidovudine therapy". Adv. Exp. Med. Biol. 398: 1310134 (1996).

[0089] Tryptophan levels can also be measured indirectly, e.g., by measuring nicotinamide adenine dinucleotide levels and/or serotonin levels. Whole blood serotonin levels can be measured, e.g., as discussed in Launay, J.M., et al. "Serotonin and human immunodeficiency viruses". Nouv. Rev. Fr. Hematol. 31(2): 159-161 (1989). Nicotinamide adenine dinucleotide levels can also be measured, according to known methods. See, e.g., Murray, M.F., "HIV infection decreases intracellular nicotinamide adenine dinucleotide [NAD]". Biochem. Biophys. Res. Commun. 212(1): 126-131 (1995).

[0090] The degree of deficiency in each various nutrient in individual patients can vary and will depend on, e.g., previous diet and disease progression. Dosage can be varied accordingly, e.g., depending on the degree of nutrient deficiency, severity of the symptoms, and the clinical judgment of a treating physician or other health service provider. Ongoing assessments of any of the above indicators, as well as, for example, weight and quality of life assessments, can also be used to determine efficacy of treatment and/or whether a change in dosage is recommended at a particular point in treatment.

[0091] In some embodiments, treatment is continued until one of more benefits is realized and/or one or more of the parameters discussed herein shows an improvement. In preferred embodiments, effective amounts of the nutraceutical composition are administered on an ongoing basis, such as, e.g., for several years, a decade or several decades, or for the rest of the infected individual's life.

[0092] The effective amount can be administered in a single dose or in a series of doses separated by appropriate time intervals, such as hours. Dosage can be daily, twice daily, three times daily, or more. In preferred embodiments, the nutraceutical compositions are administered daily, and the daily dosage is varied depending on the degree of nutrient deficiency of the individual being treated. In some embodiments, it is recommended that the dose is taken with food, e.g., where the protocol involves a thrice daily dose, the dose can be taken with breakfast, lunch, and dinner.

[0093] In some embodiments, the daily dose comprises from about 100 to about 1,000 micrograms of selenium. In some embodiments, the daily dose comprises from at least about

200, at least about 300, at least about 500, or at least about 700 micrograms of selenium. In some embodiments, the daily dose comprises less than about 400, less than about 500, less than about 700, less than about 800, or less than about 900 micrograms of selenium.

[0094] In some embodiments, the daily dose comprises from about 1 to about 4 grams of cysteine, in the form of N-acetyl-cysteine or L-selenocysteine. In some embodiments, the daily dose comprises from at least about 1.5, at least about 2, at least about 3, or at least about 3.5 grams of N-acetyl-cysteine or selenocysteine. In some embodiments, the daily dose comprises less than about 2, less than about 2.5, less than about 3, or less than about 3.5 grams of N-acetyl-cysteine or selenocysteine.

[0095] In some embodiments, the daily dose comprises from about 10 to about 25 grams of glutamine. In some embodiments, the daily dose comprises from at least about 12, at least about 15, at least about 20, or at least about 23 grams of glutamine. In some embodiments, the daily dose comprises less than about 15, less than about 18, less than about 20, or less than about 23 grams of glutamine.

[0096] In some embodiments, the daily dose comprises from about 1 to about 4 grams of tryptophan. In some embodiments, the daily dose comprises from at least about 1.5, at least about 2, at least about 3, or at least about 3.5 grams of tryptophan. In some embodiments, the daily dose comprises less than about 2, less than about 2.5, less than about 3, or less than about 3.5 grams of tryptophan.

[0097] In some embodiments, the daily dose comprises three times the amounts indicated in Table 2 below, for the corresponding nutrient components being administered. In some preferred embodiments, the daily dose is divided into three equal servings, administered three times a day, preferably with food, e.g., with each meal (breakfast, lunch, and dinner).

[0098] The nutraceutical compositions of the present invention are intended for administration to a mammal, in particular a human being, in a suitable dosage form, e.g., as known in the art. Suitable dosage forms known in the art include parenteral, enteral, oral, and the like. Preferably, the nutraceutical composition comprising a combination of nutrient components is administered orally. Oral solid and liquid dosage forms are particularly preferred.

[0099] Oral solid dosage forms are well known in the art and include powders, capsules, pills, tablets, caplets, gelcaps, and edible food items. Oral solid dosage forms can be made with one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients assist or make possible the formation of a dosage form for a bioactive material and can include diluents, binding agents, lubricants, glidants, disintergents, coloring agents, and flavorants, along with the nutrient components. An excipient is pharmaceutically acceptable if, in addition to performing its desired function, it is non-toxic, well tolerated upon ingestion, and does not interfere with absorption of bioactive materials.

[00100] Tablets can be made by well-known compression techniques using wet, dry, or fluidized bed granulation methods. The effective amounts and/or effective proportions of nutrient components disclosed herein can be combined with the desired amount of a pharmaceutically acceptable excipient (e.g. lactose, starch, dextrin, ethyl cellulose and the like) and, in the case of wet granulation, water. The ingredients can then be mixed in a blender. Useful blenders include the twin-shell type, the planetary mixer type, and the high-speed high-shear type; all of which are known to the skilled artisan. The blended combination can be sieved and dried to a granulate. The granulate can be then compressed into tablets, for example, using a tableting press as is known in the art. Preferably, the granulate is sieved before the compression to make sure that the granulate has the desired particle size. The proportion of components and excipients, binder and water (if used), etc., as well as the time and intensity of mixing, can be routinely optimized to obtain a granulate with the desired tableting characteristics. Tablets can be either coated or uncoated as is known in the art. Tablet making is well known to skilled artisan and is described, for example, by Edward Rudnic and Joseph B. Schwartz, Oral Solid Dosage Forms, in Volume II, Remington: The Science and Practice of Pharmacy, Chpt. 92, 1615, 1615-1637 (Alfonso R. Gennaro, ed., 19.sup.th ed. 1995).

[00101] Capsules, also known as dry-filled capsules, are oral solid dosage forms in which the composition is contained in a swallowable container of suitable size, typically made of gelatin. Hard empty capsules suitable for containing the nutraceutical composition of the present invention are available from several sources, for example, Tishcon Gel-Tec, 2410 N. Zion Rd., Salisbury, Md. 21801; the capsules are supplied in two halves and in various sizes. The sizes are typically designated by number. For example, 000 represents a large size commonly in use,

while 5 represents a small size commonly in use. The capsule halves can be colored by a suitable coloring agent and each half can be the same or different colors.

[00102] In making a solid oral dosage form that is a capsule, the nutrient components are combined and mixed together, with or without a diluent such as lactose, mannitol, calcium carbonate, or the like, using any of the mixers described above. Prior to mixing, a granulate of one or more of the components can be prepared as in the making of tablets. In some embodiments, organic sugar is used as a filler. In some embodiments, dessicated animal products, e.g., dessiçated beef liver (defatted or preferably undefatted) is used, both as a filler and to provide a rich source of additional amino acids.

[00103] The combined mixed components, along with any excipients and/or fillers, etc., are packed into one capsule half. The filled half-capsule is then closed with the other capsule half. Manual, semiautomatic, and automatic equipment for filling capsules are known in the art. The art of capsule filling is well known to the skilled artisan and is described, for example, by Edward Rudnic and Joseph B. Schwartz, Oral Solid Dosage Forms, in Volume II, Remington: the Sciemce and Practict of Pharmacy, Chpt. 92, 1615, 1642-1647 (Alfonso R. Gennaro, ed., 19.sup.th ed. 1995).

[00104] When the oral solid dosage form is either a tablet, gelcap, capsule, or caplet, administration can be more convenient when the nutraceutical composition is in the form of multiple oral solid dosage forms. That is, in the form of at least first and second oral solid dosage forms. The compositions of the at least first and second oral solid dosage forms can be the same or they can be different. Thus, in embodiments having multiple oral solid dosage forms, the entire effective amount and/or effective proportion of a component can be in one of the at least first and second oral dosage forms, or such effective amount and/or effective proportion can be distributed equally or unequally between each of the at least first and second oral sold dosage forms. In embodiments having at least first and second oral solid dosage forms, the effective amount and/or effective proportion of each nutrient component is preferably distributed equally among the multiple solid dosage forms

[00105] In some preferred embodiments, the effective amount and/or effective proportion of each nutrient component of a nutraceutical composition is distributed equally among three solid dosage forms, where one of each is to be taken with food, three times a day. In some particularly

preferred embodiments, the effective amount and/or effective proportion of each nutrient component is distributed equally among six solid dosage forms, e.g., six capsules, where two of each are to be taken with food, three times a day.

[00106] The oral solid dosage form used in the present invention can be a chewable food item that includes the nutraceutical composition. In addition to the nutraceutical composition, the chewable food item can and preferably does contain one or more nutrients such as soy protein isolate, soy protein hydrolysate, calcium caseinate, whey protein isolate, whey protein concentrate, milk protein isolate, skim milk powder, yogurt solids, or hydrolyzed bovine gelatin in combination with oils, binders, fillers, processing aids, and the like, as known in the art. The oral solid dosage form can be formed of a mass having the desired ingredients, and into a shape, preferably a bar having a circular, semicircular, or rectangular cross-section by, for example, extrusion, and cut into chewable food item dosage forms of about 50 to about 175 grams each, whereby each such dosage form includes an effective amount of the nutraceutical composition.

[00107] Oral liquid dosage forms can be prepared with one or more vehicles and include solutions, emulsions, and suspensions. A vehicle can be any potable substance or mixture of potable substances that are liquid at room temperature and that do not interfere with the effectiveness of the nutraceutical composition. Water, ethanol, and oils, especially vegetable oils and seed oils, are preferred vehicles. Water is a particularly preferred vehicle. Emulsions and suspensions are preferred liquid oral dosage forms. In the case of an oral liquid dosage form that is an emulsion, two vehicles having limited mutual solubility can be used.

[00108] Oral liquid dosage forms may be hybrid. In one example of an oral liquid dosage form that is a hybrid, one or more nutrient components of the nutraceutical composition, or a fraction of them, are dissolved in a vehicle, and the remainder are in suspension in the vehicle. In another example of a liquid oral composition that is a hybrid, one or more nutrient components, or any fraction thereof, of the nutraceutical composition are dissolved in a first vehicle and the remainder are suspended or dissolved in a second vehicle that forms an emulsion with the first vehicle. Other hybrid liquid oral dosage forms will be apparent to the skilled artisan and are within the scope of this invention. The making of oral liquid dosage forms is well known to the skilled artisan and is described, for example, by J. G. Narin, Solutions, Emulsions, Suspensions and Extracts, in Volume II Remington: the Science and Practice of Pharmacy, Chpt.

86, 1495, 1495-1521 (Alfonso R. Gennaro, ed., 19.sup.th ed., 1995). These oral liquid dosage forms can be ready-made, that is introduced into commerce in the liquid form in which they are to be administered. Preferred oral liquid dosage forms of the ready-made type are in the form of a beverage that can be carbonated.

[00109] Alternatively, a dry concentrate of the oral liquid dosage form can be supplied in the form of a powder that can be mixed by the practitioner or consumer with a potable liquid (e.g. milk, water, fruit juice) to form the oral liquid dosage form prior to administration. Powders can contain additives known in the art to prevent caking of the powder and maintain desirable free-flowing characteristics of the powder. In particularly preferred embodiments, the nutraceutical composition is provided as a powered drink mix, e.g., sold in packets, to be mixed into drinks for oral consumption.

[00110] In some embodiments, the nutraceutical composition comprises an enriched foodstuff. Foodstuffs may be enriched according to techniques known in the art. These include, for example, direct incorporation or by growth in enriched soils, to produce a food item or group of food items that can provide the combinations of nutrient components described herein. [[PLEASE PROVIDE ANY EXAMPLES OF THIS] Direct incorporation can include, e.g., mixing or dissolving a capsule, tablet or powder, e.g., as described above, into the food item to be consumed.

[00111] Soil enriched with one or more nutrients discussed herein can be produced according to methods known in the art. For example, soil can be enriched with selenium to reproduce or approximate the selenium soil composition of Senegal, Africa. See, e.g., Oldfield, J.E. Selenium World Atlas. Grimbergen, Belgium: Selenium-Tellurium Development Association (1999); Cowgill, U.M. "The distribution of selenium and mortality owing to acquired immune deficiency syndrome in the continental United States". Biological Trace Element Research. 56: 43-61 (1997). Also, Finnish law requires enrichment of fertilizers with selenium, and soils fertilized with such provide additional examples of desired soils.

Kits [[SHOULD WE INCLUDE KIT ASPECTS?]]

EXAMPLES

[0100] A prospective, randomized, double blinded, clinical trial was carried out, designed to determine the affects of two nutritional supplement mixtures on HIV-1 disease progression in HIV-infected patients who were not receiving any anti-retroviral treatment. These mixtures were designed to increase the body's production of glutathione peroxidase to determine whether elevated levels of this selenoenzyme changed the course of HIV infection.

[0101] The trial received ethics approval from the Mulago Ethical Review Committee (ERC) and the Uganda National Council of Science and Technology, and was given the International Standardized Randomized Controlled Trial Number 42274642. Before enrollment, informed consent was obtained from study participants, all of whom were outpatients of the Mengo Hospital in Kampala, Uganda. The trial lasted one year.

[0102] *Study Subjects and Study Site*

[0103] 310 HIV-positive patients were recruited to receive assigned supplements for 52 weeks. This study size was adequate to bring about a power of 80 percent at a 95 percent confidence interval. 249 of the enrolled patients were female and 61 male. In women, the median age at the trial's start was 36.0 years (25 percentile 30.0 years, 75 percentile 40.0 years). In men, the median age was 39.0 years (25 percentile 33.7 years, 75 percentile 45.5 years). Using a random block design to achieve patient randomization, participants were given one of two nutrient supplement combinations identified as A or B, to be taken three times daily with meals, for 52 weeks (Table 2). Patients who were pregnant, had a baseline CD4T lymphocyte count of 200 or less, or who were receiving anti-retroviral treatment were excluded from trial participation. However, patients who suffered from other additional illnesses, such as tuberculosis, were accepted for enrollment. All clinical staff and student assistants were unaware of the patient group treatment assignments. The labels were attached to all bottles of nutrients by an external co-ordinator in Canada who also kept the code necessary to identify members of the two groups. All trial participants agreed to return, at six weekly intervals, to Mengo Hospital to receive nutritional supplements and for measurement of CD4 cell counts, serum glutathione peroxidase, weight and quality of life assessments, as required.

[0104] *Study Medications*

[0105] Two nutritional combinations were designed and encapsulated specifically for use in this trial. The medications given to patients in Group B consisted of 30 nutrients with a filler of

organic sugar (Table 2). This combination of nutrients had been found, in small open trials, to stimulate appetites in HIV-positive patients. Bradfield, M., Foster, H.D.: "The successful orthomolecular treatment of AIDS: accumulating evidence from Africa". J Orthomol Med, 2006; 21(4): 193-196. The logic behind this approach was to establish whether greater appetite was sufficient to encourage HIV-positive individuals to increase their consumption of local foods to a point where enough selenium and amino acids were digested to normalize glutathione peroxidase levels. Serious loss of appetite is otherwise a common symptom of HIV/AIDS. Shabert, J.K., et al "Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized double-blind control trial". Nutrition, 1999; 15(11-12): 860-864.

[0106] The capsules taken by Group A patients contained the same thirty supplements as in Group B, but also included seven additional nutrients, as shown in Table 2. The latter nutrients were designed to directly promote the body's production of glutathione peroxidase and, in addition to amino-acid rich desiccated beef liver, included L-selenomethionine, N-acetyl cysteine, L-glutamine, hydroxytryptophan, alpha lipoic acid and ascorbic acid. Patients receiving this mixture of supplements did not have to rely on their own diet to provide the selenium, cysteine, tryptophan and glutamine thought necessary to boost body glutathione peroxidase levels.

[0107] Capsule sizes and dosages were identical and their appearances were extremely similar. Both nutritional combinations A and B were taken three times daily (six capsules in total) with food.

Table 2. Nutritional combinations used in Mengo Hospital HIV-Positive Outpatient Trial

Amount per Serving (Three servings to be taken per day)	**Group A**	**Group B**
Calcium	23 mg	23 mg
Magnesium	23 mg	23 mg
Boron	0.2 mg	0.2 mg
Zinc	1.1 mg	1.1 mg
Vanadium	2 mcg	2 mcg
Copper	100 mcg	100 mcg
Chromium	8 mcg	8 mcg
Manganese	620 mcg	620 mcg
Silica	770 mcg	770 mcg
AEP Iron (2-amino ethanol phosphate)	600 mcg	600 mcg

Amount per Serving (Three servings to be taken per day)	Group A	Group B
Iodine	2.9 mcg	2.9 mcg
Strontium	25.7 mcg	25.7 mcg
Molybdenum	0.3 mcg	0.3 mcg
Vitamin A	390 IU	390 IU
Provitamin A	390 IU	390 IU
Vitamin D_3	31 IU	31 IU
Vitamin B_1	1.9 mg	1.9 mg
Vitamin B_2	1.9 mg	1.9 mg
Vitamin B_3	7.8 mg	7.8 mg
D-Calcium Pantothenate	7.8 mg	7.8 mg
Vitamin B_6	1.9 mg	1.9 mg
Vitamin B_{12}	8 mcg	8 mg
Vitamin C (calcium ascorbate)	23 mg	23 mg
Vitamin E (D Alpha Tocopheryl Succinate)	5 IU	5 IU
Vitamin K (Phytonadione)	23 mcg	23 mcg
Biotin	8 mcg	8 mcg
Folic Acid	31 mcg	31 mcg
Choline	4 mg	4mg
Inositol	4 mg	4mg
P.A.B.A. (Para Amino Benzoic Acid)	2 mg	2 mg
Dessicated Beef Liver (undefatted)	400 mg	Nil
L-Glutamine	180 mg	Nil
Hydroxytryptophan L-S (5-HTP)	180 mg	Nil
N-Acetyl Cysteine	180 mg	Nil
Alpha Lipoic Acid	30 mg	Nil
Ascorbic Acid	40 mg	Nil
L-Selenomethionine	200 mcg	Nil
Organic sugar as a filler	Nil	Yes

[0108] *Clinical and Laboratory Evaluations*

[0109] Potential study patients underwent an initial screening at Mengo Hospital. This involved collection of demographic data, medication history and a laboratory testing of CD4T cell levels. Eligible participants then returned to this hospital for baseline and follow-up visits on a six weekly basis for 52 weeks. Glutathione peroxidase levels were measured at baseline on entering the trial, after 30 weeks and at the end of the trial, as were CD4+ T cell counts. Laboratory measurements of serum glutathione peroxidase levels took place at the Mengo Hospital Laboratory, while CD4T cell counts were conducted by the Hematology Laboratory at Mulago Hospital. Patients were also weighed during each of their hospital visits. Karnofsky quality of life scores were taken at baseline and at 30 and 52 weeks.

[0110] *Data and Collection and Statistical Analyses*

[0111] At Mengo Hospital, patient data was stored in an Access database and data collection forms were created using Access database software. After collection, the data were moved from Access to the statistical package SPSS for analyses.

[0112] All statistical analyses were conducted by the Statistical Consulting Centre of the University of Victoria, British Columbia, Canada, which recommended the use of Wilcoxan Signed Ranks Tests and the Sign Test to establish the statistical significance of data from baseline to the study's 52 week conclusion. SPSS Inc. SPSS base 15.0 Use's Guide. Chicago: SPSS Inc. 2006.

[0113] The study's primary end points were to examine the effects of the two nutrient mixtures on serum glutathione peroxidase levels and on CD4 cell count. Secondary end points were weight changes and general health status as measured by Karnofsky scores. Of particular interest was any delay in the progression of AIDS and the need to start associated anti-retroviral treatment.

[0114] *Results*

[0115] 310 patients began the trial, 160 of whom were randomly assigned to Group A and 150 to Group B. During its 52 week duration, 47 patients exited the program, 29 from Group A and 18 from Group B. This represented a loss to follow-up of some 15.2 percent. In Group A, 3 left because of pregnancy, 14 were lost to follow-up, 4 withdrew consent, 2 died from tuberculosis and one from esophageal cancer. Two further patients died from unknown causes and another from severe anemia. In Group B, over the course of the trial, one patient left because of pregnancy, 6 were lost to follow-up, one withdrew consent, four died of tuberculosis, two from cancer and four of undiagnosed illnesses.

[0116] As a consequence, 81.9 percent of patients in Group A and 88.0 percent of those from Group B completed the year long trial. The statistical analyses which follow refer to these patients. Beyond simple measures of central tendency, Sign Test and Wilcoxan Signed Rank Tests were used to establish whether the obtained results were statistically significant, at least at the 0.01 level.

[0117] *Immunological, Biochemical Parameters*

[0118] From baseline over the one year period of follow up, 92 patients in Group A experienced an increase in CD4 count, while the remaining 39 showed a decrease (Table 3). Nevertheless, the mean/median CD4 count for Group A as a whole rose from 400/347 to 446/388 cells/mm^3. The Wilcoxan Signed Ranks Test and the Sign Test both indicated that the mean/median increases were statistically significant ($p = 0.000$) for Group A.

[0119] Similarly, from base measurement to week 52, 89 patients in Group B showed an increase in their CD4 counts, while the remaining 41 displayed a decrease. The mean/median CD4 count for Group B rose from 400/335 to 446/394 over the year. Again the Wilcoxan Signed Ranks Test and Sign Test both indicated that these gains were statistically significance ($p = 0.000$).

[0120] At the beginning and end of the 52 week trial, glutathione peroxidase levels were measured in 92 patients from Group A. 77 of these patients experienced an increase in the serum levels of this selenoenzyme, while the remaining 15 showed decreases. As a whole, 92 patients in Group A, for whom serum glutathione peroxidase levels were measured, showed mean/median increases from 3825/3628 U/L at the beginning of the 52 week long trial to 8894/8573 U/L at its end ($p = 0.000$). Similarly, serum glutathione peroxidase levels were measured in 92 members of Group B at the start and endpoint of the trial. 81 of these had experienced an increase and 11 a decrease in serum levels of this selenoenzyme. This group, as a whole, showed rises in mean/median serum glutathione peroxidase levels from 3862/3602 U/L to 9839/9203 U/L over the 52 week trial. Both the Sign Test and Wilcoxan Signed Rank Test established that these increases were of statistically significance ($p = 0.000$).

Table 3. Changes (increases/decreases/no change) in CD4+ T cell counts, serum glutathione peroxidase, weight and Karnofsky scores from baseline measurement to 52 weeks.

Group A		CD cell count	Serum glutathione peroxidase	Weight	Karnofsky Score
	Increase	92	77	69	68

	No Change	0	0	17	27
	Decrease	39	15	41	34
Group B					
	Increase	89	81	76	71
	No Change	0	0	8	27
	Decrease	41	11	42	31

[0121] *Clinical Parameters*

[0122] Over the 52 weeks, 67.7 percent of the patients in Group A either increased, or remained the same in weight. Mean weight increased from 60.1 kg to 61.1 kg. Both the Wilcoxan Signed Rank Test ($p = 0.001$) and the Sign Test ($p = 0.01$) showed this gain to be statistically significant. Similarly, 66.7 percent of the patients in Group B either increased or remained the same in weight over the year long trial. Mean weight for Group B rose from 62.0 kg to 63.4 kg, during the 52 weeks. Again both Wilcoxan Signed Ranks Test ($p = 0.000$) and the Sign Test ($p = 0.002$) demonstrated that weight gain was of statistical significance.

[0123] Quality of life, as measured by the Karnofsky scores, also had risen during the duration of the trial in both groups. In Group A, for example, these scores rose or remained the same in 73.6 percent of patients, while the mean of this measure increased from 81 to 85 ($p= 0.000$ and $p = 0.001$). In Group B, scores rose or remained unchanged in 76.0 percent of patients, while the mean rose from 82 to 86 ($p = 0.000$ in both statistical measures).

[0124] Moreover, many patients reported significant appetite i ncreases, together with the return of their ability to walk long distances. Most also reported being happier. The quantitative data supported these reports.

[0125] *Comparison of Groups A and B and of Males and Females*

[0126] Four Analysis of Variance (ANOVA) models were used to compare changes in CD4 cell counts, serum glutathione peroxidases, weight and Karnofsky scores, over 52 weeks, using two factors: nutritional combinations and gender. Neither of these two factors were significant at the 0.05 level. That is, during this trial, there were no statistically significant gender differences in the results obtained, nor were there any statistically significant differences in changes in CD4 cell count, serum glutathione peroxidase, weight or Karnofsky scores between Group A and B patients. In summary, both genders showed similar immunologic, biochemical and clinical improvements, regardless of which of the two nutritional combinations they were taking.

[0127] *Summary of Results*

[0128] In the trial described here, two nutritional treatments were able to increase serum glutathione peroxidase levels in HIV-infected outpatients by roughly a factor of 2.5, over a 52 week period. Such increases would be very unexpected in HIV-positive patients who are not receiving anti-retroviral drugs, since serum selenium and glutathione peroxidase levels both normally decline as HIV/AIDS progresses. Dworkin, B.M. "Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS)". Chem Biol Interact, 1994; 91(2-3): 181-186; Look, M.P., et al. "Serum selenium, plasma glutathione (GSH) and erythrocyte glutathione peroxidase (GSH-PX) levels in asymptomatic versus symptomatic human immunodeficiency virus-1 (HIV-1) infection." Eur J Clin Nutr, 1997; 51(4): 266-272.

[0129] Simultaneously, the CD4+ T cell counts, indicative of an improving immune system, rose in both treatment groups. Such improvements are also atypical of HIV-positive patients not taking anti-retroviral drugs. To illustrate, a healthy CD4+ T cell count is somewhere between 500 and 1500 cells per cubic millimeter of blood. Normally, as observed at Mengo Hospital and confirmed elsewhere, in HIV-positive patients not receiving anti-retroviral, the count decreases on average about 50 to 100 cells each year. AIDS Meds. Corn T-cell Test. http://www.aidsmeds.com/articles/TCellTest_4727.shtml. If this is the case, one might have expected CD4+ T cell counts (mean/median) to have fallen to some 325/272 in patients in Group

A and 325/260 in Group B after the completion of the 52 week trial. In fact, these measures of central tendency were, as described, 446/338 and 446/394 at trial's end. That is, both nutrient groups had mean and median CD4+ T cell counts that were roughly 120 cells per cubic millimeter of blood higher than expected in HIV-positive patients not receiving antiretroviral treatment. Increases in weight and Karnofsky Score were also indicative of a general clinical improvement in health of both treatment groups.

[0130] This trial shows that both nutrient combinations (Table 2), taken for 52 weeks by HIV-positive patients who were receiving no anti-retroviral drugs, can significantly slow their decline into AIDS. Improvement is associated with increases in serum glutathione peroxidase levels, CD4 cell counts, body weights and in quality of life scores. This impressive overall improvement indicates the need for correct combinations of nutrient supplements in treating the diverse symptoms and conditions associated with AIDS.

[0131] All patents, patent publications, and other publications referred to herein are hereby incorporated by reference, to the same extent as if each individual publication, patent, or patent publication was specifically and individually indicated to be incorporated by reference.

[0132] Certain modifications and improvements will occur to those skilled in the art upon a reading of the foregoing description. It should be understood that all such modifications and improvements have been deleted herein for the sake of conciseness and readability. Nonetheless, all such modifications and improvements are contemplated as within the scope of the instant invention and are properly within the scope of the following claims.

We claim:

1. A neutraceutical composition for alleviating symptoms of acquired immune deficiency syndrome, comprising a selenium component, a cysteine component, a glutamine component, and a tryptophan component.

2. The neutraceutical composition according to claim 1, wherein said selenium component and said cysteine component comprise at least [50%] selenocysteine.

3. The neutraceutical composition according to claim 1, wherein said neutraceutical composition comprises from about 100 to about 1000 micrograms of selenium, from about 1 to about 4 grams of cysteine, from about 10 to about 25 grams of glutamine, and from about 1 to about 4 grams of tryptophan..

4. The neutraceutical composition of claim 1, further comprising a vitamin component, wherein said vitamin component comprises one or more of vitamin A, niacin, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin D, vitamin C, vitamin E, vitamin K, biotin, and folic acid.

5. The neutraceutical composition according to claim 4, wherein said vitamin component comprises one or more of niacin, B1, B6, C and/or E.

6. The neutraceutical composition according to claim 5, wherein said vitamin component is selected from the group consisting of B1, B6, C and/or E.

7. The neutraceutical composition according to any one of claims 1 to 6, further comprising a second/additional mineral component; wherein said second mineral component comprises one or more of calcium, boron, copper, chromium, manganese, magnesium, zinc, sulfur, molybdenum, vanadium, iodine, iron and strontium.

8. The neutraceutical composition according to claim 7, wherein said second mineral/component comprises one or more of magnesium, zinc and sulfur.

9. The neutraceutical composition according to claim 7, wherein said second mineral component is selected from the group consisting of magnesium, zinc and sulfur.

10. The neutraceutical composition according to claim 7, further comprising one or more of inositol, choline, para-amino benzoic acid and silica.

11. A method for methods for correcting enzyme deficiencies in a patient in need thereof, comprising administering to said patient a neutraceutical composition according to any one of Claims 1-10.

12. The method according to claim 11, wherein said patient has or is suspected of having a viral infection.

13. The method according to claim 12, wherein said patient is HIV-positive.

14. A method for preventing and/or alleviating the clinical symptoms of Acquired Immune Deficiency Syndrome in an HIV-positive patient, comprising administering to said patient a neutraceutical composition according to any one of Claims 1-10.

15. A method of increasing CD4+ T cells in an HIV-positive patient, comprising administering to said patient a neutraceutical composition according to any one of claims 1 to 10.

ABSTRACT

The present invention provides nutraceutical compositions containing a combination of nutrients, including selenium, one or more of cysteine, glutamine and tryptophan, and optionally additional nutrient supplements. The compositions find use in nutritional methods of treating and/or preventing conditions commonly associated with AIDS. The methods generally involve oral administration of the nutraceutical composition to an HIV-infected individual.

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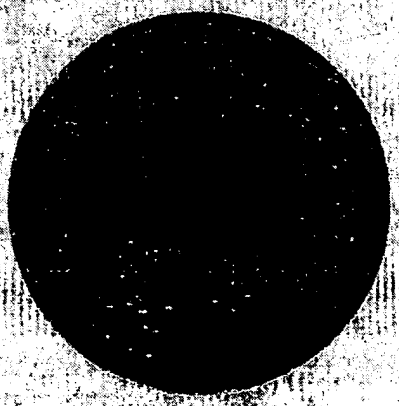

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When the Nutritional Supplements Stop: Evidence from a Double-blinded, HIV Clinical Trial at Mengo Hospital, Kampala, Uganda

Edith Namulema, M.BchB; M.Sc. Epid.[1] James Sparling, M.D.,[2]
Harold D. Foster, Ph.D.[3]

Introduction

Last year, in this journal,[1] the authors reported on the results obtained in a prospective randomized, double-blinded clinical trial, involving 310 HIV-infected outpatients of Mengo Hospital, Kampala, Uganda. In this registered trial (International Standardized Randomized Controlled Trial Number 42274642), patients with baseline CD4 cell counts above 200, who were not receiving anti-retroviral drugs, were placed randomly into Groups A and B. The medications given to patients in Group B consisted of 30 nutrients with a filler of organic sugar. This combination of nutrients had been found, in small open trials, to stimulate appetites in HIV-positive patients.[2] The logic behind this approach was to establish whether greater appetite was sufficient to encourage HIV-positive individuals to increase their consumption of local foods to a point at which enough selenium and amino acids were digested to normalize glutathione peroxidase levels. Serious loss of appetite is a common symptom of HIV/AIDS.[3]

The capsules taken by Group A patients contained the same thirty appetite stimulating supplements, but also included an additional seven nutrients. The latter nutrients were designed to directly promote the body's production of glutathione peroxidase and, in addition to amino-acid rich desiccated beef liver, included L-selenomethionine, N-acetyl cysteine, L-glutamine, hydroxytryptophan, alpha lipoic acid and ascorbic acid. Patients receiving this mixture of supplements did not have to rely on their own diet to provide the selenium, cysteine, tryptophan and glutamine thought necessary to boost body glutathione peroxidase levels.[4]

Results of Initial Trial

The year long study[1] examined the effects of these two combinations of nutrients on biochemical and immunologic parameters, that is, serum glutathione peroxidase levels and CD4 cell counts as the study's primary endpoint. Secondary endpoints were weight changes and patient assessed quality of life.

The mean/median serum glutathione peroxidase levels in Group A (37 nutrients) increased from 3825/3628 IU/L (International Units) at baseline to 8894/8575 IU/L at the trial's end ($p<0.000$). Similarly, patients in Group B (30 nutrients) had an increase in mean/median serum glutathione peroxidase levels from 3862/3602 to 9839/9203 IU/L over the length of the trial ($p<0.000$). The mean/median CD4 cell counts rose from 400/347 mm^3 to 446/388 in Group A and from 400/335 to 446/394 mm^3 in Group B ($p<0.000$). Mean weight increases over 52 weeks were 1.0 kg in Group A and 1.4 kg in Group B, while Karnofsky scores in Group A rose from 81 to 85 and in Group B from 82 to

1. Principal Investigator, Program Manager, AIDS Clinic, Mengo Hospital.
2. Internal Medicine and Respiratory Disease, Victoria, BC and Board Member, The Friends of Mengo Hospital (Canada).
3. Professor, Department of Geography, University of Victoria, PO Box 3060, Victoria, BC, Canada, V8W 3R4.
The initial trial was supported in full by the Canadian charity, The Friends of Mengo Hospital.
Correspondence Address: Harold D. Foster, PhD., Department of Geography, University of Victoria, PO Box 3060, Victoria, BC, Canada, V8W 3R4. Email: hdfoster@shaw.ca

86. Wilcoxan Signed Ranks Test and the Sign Test both indicated that all these measured increases within both groups were statistically significant ($p<0.01$). Indeed, for both glutathione peroxidase levels and CD4 cell counts $p<0.000$ in all cases. There were, however, no statistically significant differences between the measured parameters, (serum glutathione peroxidase, CD4-cell counts, weight and Karnofsky scores) in Group A compared with those of Group B ($p>0.05$), or between males and females ($p>0.05$).

Post-Trial Results

The year-long double-blinded clinical trial was funded by the Canadian charity, The Friends of Mengo Hospital. This allowed information on serum glutathione peroxidase levels, body weights and Karnofsky scores to be assessed six months after the trial had formally ended. CD4 cell counts were also measured at the same time, as part of normal hospital procedures.

This additional data allowed an assessment of the health implications of discontinuing nutritional supplementation in HIV-positive patients. To illustrate, the initial double-blinded closed year long trial began with 310 patients, 263 of whom completed it (84.8%). At the end of the six month open, post-trial study, CD4 cell counts were available for 213 of these patients and serum glutathione peroxidase levels from 122. Karnofsky quality of life scores also had been collected for 191 of the former participants in the closed trial and body weight for 166.

Six months after the formal closed trial had ended, the mean/median serum glutathione peroxidase levels of the 124 assessed patients had fallen by 7117/5184 IU. ($p<0.001$). During this time period, of course, former members of Group A and Group B had not been provided with any nutritional supplements. This decline in serum glutathione peroxidase levels in this group was almost universal.

Similarly, in the 213 patients for whom CD4 cell counts were available at the end of the six month post-trial period, mean/median levels had fallen by 155/151 mm^3 respectively. ($p<0.001$). Similarly, in the 191 patients that had their mean/median Karnofsky quality of life scores assessed six months after the closed trial had ended, these had fallen by 5.5/5.0 respectively ($p<0.001$).

It is clear that dramatic falls in serum glutathione peroxidase levels, CD4 cell counts and Karnofsky scores had occurred during the six months in which nutrient mixtures A and B were no longer available to former closed-trial patients. Unfortunately, these losses during the post-trial period had more than negated all the gains in quality of health indicators that most patients had achieved during the nutritional trial itself. Additional analyses indicated that such declines had occurred in the post-trial period, regardless of the nutrient group to which the patient had formerly belonged. Similarly, gender difference made no statistically significant difference ($p>0.05$).

The only exception to this generalization involved body weight. During the six month period nutrient supplements were not provided, former trial participants had lost relatively little weight. In the 166 patients for whom this measure was available, mean/median weight had only fallen by 0.61/0.00 kilograms ($p>0.05$).

Conclusions

The initial prospective randomized, double-blinded clinical trial demonstrated that two nutrient mixtures taken for 52 weeks by HIV-positive patients who were receiving no anti-retroviral drugs, significantly slowed their decline into AIDS. The improvement was associated with increases in serum glutathione peroxidase levels, CD4 cell counts, body weight and improvements in quality of

life scores. In contrast, the post-trial data demonstrated that if such supplementation stops, HIV-positive patients suffer a rapid health decline. This involves highly statistically significant drops in serum glutathione peroxidase levels, CD4 cell counts and Karnofsky quality of life scores ($p<0.001$). These results are very consistent with those of smaller open trials using nutritional supplement which have been conducted elsewhere in Sub-Saharan Africa.[5] It seems clear that inadequate nutrition plays an extremely important role in the progression of HIV-infected patients into AIDS. These results also are consistent with Foster's model[6] of the development of AIDS which suggests that deficiencies of glutathione peroxidase play a key role in the process.

Acknowledgements

The authors would like to thank the Canadian charity, The Friends of Mengo Hospital (Canada) for funding the initial clinical trial and the counsellors and nurses of the AIDS Clinic, Mengo Hospital, Kampala, Uganda who made this study possible. They are also indebted to monitors Natalie Ward, Peter Hunt, Alan Lingwood, Magnus McNab, Matthew King, Josh Lam and Emily Skelton. All the glutathione peroxidase analyses were undertaken at the Mengo Laboratory under the supervision of Raymond Woods. Staff at the Hematology Laboratory at Mulago Hospital established patient CD4T lymphocyte counts. Statistical calculations and tests were carried out by Dr. Nicholas Karlson, Coordinator, University of Victoria Statistical Consulting Centre. His help is greatly appreciated.

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The Successful Orthomolecular Treatment of AIDS: Accummulating Evidence from Africa

Marnie Bradfield, BScN, M.A.;[1] Harold D. Foster, Ph.D.[2]

Working Hypothesis

As shown by Dr. Will Taylor and his colleagues[1] at the University of Georgia, HIV encodes for one of the human glutathione peroxidases. As a result, as it is replicated it deprives HIV-seropositive individuals of the selenoenzyme glutathione peroxidase and its four key components, namely selenium, cysteine, glutamine and tryptophan.[2,3] Slowly but surely, this depletion process causes severe deficiencies of all these nutrients. Their lack, in turn, is behind the major symptoms of AIDS, including the collapse of the immune system, increased susceptibility to cancer, myocardial infarction and depression, muscle wasting, diarrhea, psychosis and dementia. As these nutrient deficiencies cause failure of the immune system, associated pathogenic co-factors become responsible for their own unique symptoms, such as tuberculosis, pneumocystis carinii pneumonia and toxoplasmosis.[4] Any successful treatment for HIV/AIDS, must therefore, include normalization of body levels of glutathione, glutathione peroxidase, selenium, cysteine, glutamine and tryptophan.

Clinical Trials

Initially, an attempt was made to test this hypothesis the cheapest way possible, by developing a simple nutrient mixture of selenomethionine and beef liver. This, for example, was used in open trials in a South African hospice where five of six AIDS patients greatly improved when provided with it.[5] Another small trial took place in a Kenyan clinic. Here the patients were weak and passing into AIDS. They soon recovered their energy and regained their health when given selenium and desiccated beef liver.

Encouraged by such results two further larger open trials were set up. In Zambia, the nutritional supplements were given to a child care and adoption society. As previously described in this journal,[5] 15 orphans and guardians who were HIV/AIDS patients experienced dramatic improvement when given this selenium-amino acid enriched nutrient mixture. Most showed noticeable improvement in the second to third weeks after receiving these supplements. Their complexions, hair texture and energy levels improved and their mobility increased. Some that had been bedridden began to walk. In Uganda, at the Mengo Hospital in Kampala, a 40 HIV/AIDS patient open trial also was set up. After one month, 77 % of these patients reported noticeable health improvement. These results were better than they seemed at first glance since seven patients also had tuberculosis and four had syphilis. One patient who had been bedridden for four years was able to walk from his home to the hospital to ask for more nutrients when his month's supply was exhausted.

The success of these open trials encouraged Dr. Jim Sparling to assist in establishing a 318 patient double blinded clinical trial in Uganda at the Mengo Hospital, Kampala. This is ongoing but almost completed and the results will probably be available early in 2007. Since the Ugandan authorities would not allow the use of a placebo, one of the authors (Foster) developed a nutrient mixture, called Nutramiracle® which was thought likely to be an optimum treatment for HIV/AIDS. Designed to stimulate the

1. 3400 Woodburn Avenue, Victoria, BC V8P 5C1
2. Department of Geography, University of Victoria, BC, Canada e-mail: hfoster@office.geog.uvic.ca

immune system and to correct all AIDS associated nutritional deficiencies, this mixture contained desiccated beef liver, selenomethionine, L-glutamine, hydroxytryptophan (5-HTP), N-acetyl cysteine and cofactors of glutathione peroxidase such as alpha lipoic acid and ascorbic acid. In addition, Nutramiracle® included 30 other nutrients, designed to replace losses due to diarrhea. Half of the patients in the Mengo trial received Nutramiracle.® The other 50% of patients were given 30 nutrients, that did not include either selenium or desiccated beef liver.

Soon after the start of the double blinded hospital trial in Uganda, the authors of this article met for the first time and Marnie Bradfield took samples of Nutramiracle® to Africa. Her formal education had been in Public Health Nursing and teaching English as a second language. Since Marnie's family has business interests in South Africa, she has traveled to, and throughout sub-Saharan Africa since 1970. Her mission in Africa was to give Nutramiracle® to dying AIDS patients who were not receiving other forms of medication. What follows is her description of the results of this project.

In 2003, Gilbert, an employee of our small company in South Africa, asked to go home to Zimbabwe to bury his brother saying "they said my brother has died of HIV/AIDS". When Gilbert returned to Johannesburg he was distraught and reported that his sister-in-law, Sibongile, had been "unable to come to the grave". She too had AIDS and was "lying on the floor dying." As a result, Gilbert was about to become the guardian of the three minor children in Sibongile's family.

I had read Dr. Foster's book online (http://www.hdfoster.com) and felt sure that the orthomolecular approach he suggested could cause no harm to the people that I was meeting during my months in South Africa where in some regions the level of soil selenium is among the lowest in the world. When Gilbert came to me in great consternation and distress about the state of Sibongile and her family, I asked him if he wanted to take some of Dr. Foster's 'Muti' (a generic term for medicine among Ngune speaking people). He agreed and we found a way to quickly send a bottle of Nutramiracle® to Zimbabwe. Within a few weeks we heard from other relatives that this woman who had been moribund, seemed to be improving. Over the next several weeks, Sibongile continued to get better and was later able to move to her own room and to begin to look after her children, cooking for them and taking them to school. Sibongile took Nutramiracle® for one month and then continued to receive 400 mcg of selenium each day. Her recovery is viewed by her African neighbours and friends as nothing short of a miracle. As far as is known, Sibongile is celibate. In 2004, she began to feel unwell but quickly recovered when given a further monthly course of Nutramiracle.® This was followed by a resumption of 400 mcg of daily selenium.

In November 2004, Gerson, a 44-year-old painter, employed by my family's business, became ill and almost certainly was suffering from AIDS. Later he said in his own words, "I was weak, weak... like a feather, the wind could blow me over. I was slowly dying." I spoke to Gerson and started him on the first series of Nutramiracle.® By the time he began he was seriously ill, unable to eat, very thin and lying on the floor. If he could not manage to take three tablets a day, he would take two or what was possible. I told him that I needed to know each day how many capsules he had taken, at what time and how he felt and gave him a calendar on which to note this information. He faithfully did this and much to his amazement, later told me that he knew within four or five days that he was "getting better." As he said on a filmed interview "I said these pill...they work...they very good."

Gerson took a one month course of Nutramiracle® and then began to receive 400 mcg of selenium each day. However, after a few months he appeared to be increasingly less well and was given a second series of Nutramiracle.® Since that time he has been on selenium 400 mcg daily and as of August 29, 2006 he was healthy and back at work. However, a note from another African woman in October tells me that Gerson sometimes "forgets to take his Muti" (selenium... and only remembers when he does not feel well." Such is the nature of compliance in chronic disease!

In January 2005, a 19-year-old employee, Victor, failed to return to work after the long Christmas holiday. His brother, who was also an employee (who had gone home on holiday on December 5, 2004) announced that Victor had tuberculosis but that something else was wrong because he was losing a lot of weight and had no strength. Our company could not get anyone up to see Victor for three months or so as he lived five hours up the Great North Road to Zimbabwe. Finally, Gilbert the company driver, was able to go. When he went to take the Nutramiracle® and food and other provisions to Victor, Gilbert returned with very sad news. Gilbert said he was sure Victor would die. He was living with his mother, who was spoon-feeding him. Victor "had no flesh on his body... he could not stand...he could not even sit on the chair." On June 22, 2005 the driver Gilbert, myself and my husband went to see Victor where he lives up near the Zimbabwe border. Victor's brother had reported that Victor was much better although he "was having an upset stomach" from taking the Nutramiracle.® Victor, who did not know we were coming, was sitting out in the sunshine and got up to walk to meet us at our car using a walker that we had sent him. Victor said he was much better, although he "was having an upset stomach" from taking the Nutramiracle.® (Hence, I developed a simple protocol for "muti" ingestion whereby the patient ate some food, took the Nutramiracle,® and then more food, in addition to marking the calendar notations). This may seem very simple, but life in the developing world is fraught with challenges that oftimes deter from following even basic routines. Victor has severe footdrop in his left foot and thus far this has not been corrected. However, he was well enough to undertake the five hour journey to Johannesburg in June and was then walking with one stick only. It is possible that Victor may have received some anti-retrovirals on a visit to hospital to treat his tuberculosis but, if so, they were not given to him outside the institution. The great bulk of his improvement in health appears to have been caused by Nutramiracle® and the subsequent use of selenium.

In addition, John, a 28-year-old hard working labourer, took to staying in his bed about every third day. He simply could not get up and if he did was too weak to work. He had a deep rasping cough and was rapidly becoming a skeletal in appearance. In October of 2005, I went to talk to him about his health. He agreed that "I am not good...and I have my children, they will have no one if I die." I suggested to John that he start a course of Nutramiracle.® He took the orthomolecular nutrient mixture for one month. Within a week, John has improved dramatically and was able to get out of bed and come to work even in the extreme heat of the sub-Saharan summer. John received a one month course of Nutramiracle® and, thereafter, received 400 mcg of selenium daily. He is still in good health and working.

Shortly after John began to recover, in early November 2005, I noticed that Prince, a conscientious and excellent worker, began to show symptoms of

AIDS. He dramatically lost weight and rapidly became exhausted early in the day and often had to go home to bed. I went to talk to him about his health and asked him if he would take the "muti" (Nutramiracle®)... and try it. He took Nutramiracle® for one month, and then came back to me, as he knew there was something else he needed to take. I gave him his first bottle of selenium and now he takes 400 mcg daily.

My sister-in-law who had been away during the time Prince was really ill was simply amazed when she saw him on her return. Again, he walked across the lawn, to the garden to do his work...and she said "Now who is that"? (Sometimes one's employees will bring a relative or someone to work with them). When I told her it was Prince, she could hardly believe that he was so energetic and had put on so much weight. As of October 12, 2006 he is alive, well and working.

Albert, John's brother, was also a family employee. In December, 2006, he was working outside my cottage and I realized that he had lost a lot of weight... and was moving slowly. He had continued to come to work when he could, but was rapidly deteriorating. When he came to the door of the cottage, I went out and spoke to him. He said "Oh Missus I can't eat... food not taste good...I feel bad... weak." The muscles on Albert's arms had deteriorated a lot and he was actually very frail. In this case, he asked me if he could have some "muti like you gave John". We agreed that he should start on a course of Nutramiracle® which he took for one month and then subsequently went onto the selenium maintenance dose. One morning in early January, I went out and asked him how he was feeling. His face lit up in a huge smile...and he said "Great... great...can eat lots...can work lots." As of my last update on Albert, in October 2006, he was doing well, working and taking his daily selenium supplements.

Conclusion

Several conclusions appear obvious from the African nutritional trials being used to test the efficacy of selenium and amino acids as a treatment for HIV/AIDS. Firstly, it is possible to reverse all the symptoms of AIDS in dying patients using nutrition alone. Secondly, this requires selenium and the amino acids, cysteine, tryptophan and glutamine. Thirdly, while selenium alone can slow HIV replication, eventually HIV/AIDS patients also need amino acid supplements. These can be given temporarily until deficiencies are corrected. The patients can then return to selenium supplementation alone for several months, until the more complex nutritional mixture is again required for another month. There appear to be no adverse side affects from these nutritional treatments and patients are delighted with their greatly improved health status.

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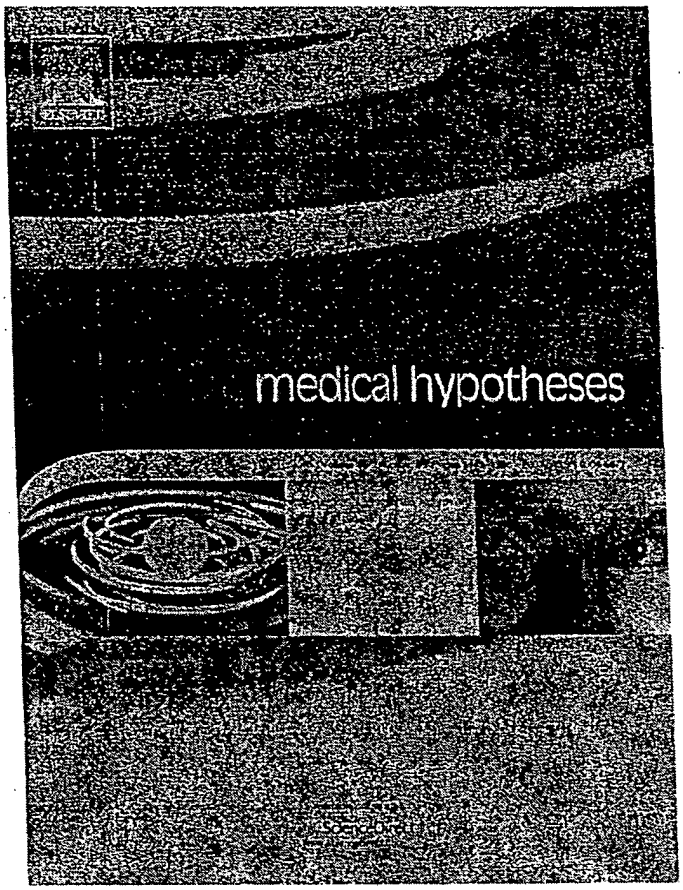

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A role for the antioxidant defense system in preventing the transmission of HIV

Harold D. Foster *

Department of Geography, University of Victoria, P.O. Box 3050, Victoria, BC, Canada V8W 3P5

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Summary Twenty-five years of experience with the human immunodeficiency virus (HIV) have established that it is relatively difficult to transmit. The chance of medical personnel acquiring this virus by needlestick injury is only 0.3%. Similarly, the odds of an HIV-positive male infecting a female partner during one unprotected sexual encounter is 9 in 10,000. Furthermore, the per-act risk of infection from penal–anal intercourse with an HIV-positive male partner is established at 82 in 10,000. Since those who are not infected by such exposures do not develop antibodies against HIV, there must be an earlier line of defense. The global diffusion pattern of HIV/AIDS is strongly suggestive of a protective role for the trace element selenium. It is hypothesized here that the body's antioxidant defense system, especially the selenoenzyme glutathione peroxidase, acts as an initial defense against viral infection, preceding the formation of antibodies. For this reason, HIV is having its greatest difficulty in infecting those with diets elevated in amino acids and the trace element selenium which, when eaten together, stimulate the body's production of glutathione peroxidase.

Introduction

Healthcare workers have often been accidentally exposed to the blood and body fluids of HIV-positive patients [1]. Needlestick injuries are relatively common, as are other types of percutaneous injury. Analysis of surveillance data suggests that the chance of transmission of HIV by this type of accidental exposure is only 0.3% [2], although the seroconversion rates are probably considerably more for deep wounds, perhaps reaching as high as 20% [3]. As a result of this low rate of transmission, by the end of 1995, only 79 cases of occupationally acquired HIV infection had been identified worldwide [2]. Unfortunate as such infections are, it is clear that healthcare workers, although often exposed to HIV-contaminated blood and body fluids, very rarely suffer work-related HIV infection.

It has been estimated that the odds of an HIV-positive male infecting a female partner during one unprotected sexual encounter is some 9 in 10,000. These odds are even lower for female-to-male infection [4]. Wawer et al. [5], for example, studied rates of HIV-1 transmission per coital act between Ugandanese couples, in which one partner is infected. They showed that the average rate of HIV transmission was 0.0012 per coital act, but varied with the time since seroconversion of the infected partners. Transmission risk was highest when the HIV-positive partner had developed AIDS.

* Tel.: +1 250 721 7331; fax: +1 250 721 6216.
E-mail address: hfoster@office.geog.uvic.ca

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In such cases, the risk of infection of the viral free partner was 0.0036% with each act of unprotected vaginal intercourse. It is clear, therefore, that the great majority of heterosexual encounters, even where the infected partner carries high viral loads, do not result in HIV transmission. This, of course, must be why despite years of unprotected sexual intercourse, most HIV-positive hemophiliac husbands did not infect their wives with the virus [6].

There is strong evidence that penal–anal intercourse, without the use of a condom, is associated with a higher risk of HIV infection, especially when trauma occurs. Nevertheless a study by Vittinghoff et al. [7] estimated the per-act risk of HIV infection from such intercourse with an HIV-positive partner at 0.82% (82 in 10,000). This estimate was based on 2633 person years of data, collected from 2180 high risk homosexual and bisexual men in San Francisco, Denver and Chicago.

Given the difficulty with which HIV is transmitted, it is widely believed that a high prevalence rate for HIV/AIDS must be a clear indication of widespread local promiscuity. However, the first comprehensive global study of sexual behaviour, recently conducted by Wellings et al. [8] appears to demonstrate that this belief is largely a myth. These researchers, from the London School of Hygiene and Tropical Medicine, analysed sexual behaviour data from 59 countries, discovering that, contrary to popular belief, single men and women in Africa are fairly inactive sexually, only two-thirds reporting recent sexual activity as compared with three-quarters of their developed country counterparts. This confirms the position taken by Van Look, director of Reproductive Health and Research at the World Health Organization. Van Look [9] is quoted as saying "there's a misperception that there's a great deal of promiscuity in Africa, which is one of the potential reasons for HIV–AIDS spreading so rapidly. But the view is not supported by the evidence".

The hypothesis

While the rates of condom use [10] and circumcision [11] vary and so influence HIV/AIDS prevalence, it seems likely that there is a more fundamental mechanism or mechanisms that control HIV transmission rates. The very low probability of infection from a single exposure, whether through needlestick, or vaginal or anal intercourse, raises an extremely significant question, "What is it that protects the uninfected, but exposed, individual from HIV?" Clearly, since seroconversion, the development of antibodies to HIV, may take anywhere from a week to several months to occur [12], the great majority of individuals exposed to, but not infected by HIV, must be protected from the virus by one or more alternative mechanisms. This article provides evidence that suggests that glutathione peroxidase, a significant selenoenzyme in the antioxidant defense system, plays this role.

Evaluation of the hypothesis

Since programmes calling for fidelity, chastity and the use of condoms are not enough, interesting spatial patterns are becoming obvious in the spread of HIV [13,14]. In countries, such as Zaire, Uganda, Tanzania, Kenya and South Africa, where AIDS is now probably the number one cause of death, soil selenium deficiency is common [15–18]. In contrast, the soils of Senegal are derived from marine sediments containing phosphorites that are selenium enriched [19]. Despite widespread unprotected promiscuity in Senegal, HIV-1 has only diffused very slowly. Amongst the Senegalese UNAIDS estimated that, as of 2001, this country had an adult HIV-prevalence of only 0.5% [20].

The relationship between soil selenium levels and the diffusion of HIV has not been limited to sub-Saharan Africa. In South America, HIV infection rates are abnormally low in Bolivia [21], a major exporter of selenium. Similarly, although selenium deficiency is common in Scandinavia, HIV infection rates are depressed in Finland [22] where the addition of selenium to fertilizers was mandated in 1984 [23]. Estonia, a selenium deficient neighbour, has an HIV-prevalence rate amongst adults that is eleven times that of Finland. A similar relationship has been demonstrated in the United States, where Cowgill [24] has documented an inverse relationship, especially in the Black population, between mortality from AIDS and local selenium levels in fodder crops.

There may be several reasons why susceptibility to HIV transmission is greatly affected by the selenium intake of the local population. This trace element is essential for the effective functioning of the immune system [25]. This author has argued [26] and demonstrated [24–28] that AIDS is the name used to describe the symptoms caused by the extreme depletion of selenium, cysteine, tryptophan and glutamine in those who are HIV-positive. This multiple nutrient deficiency, however, does not explain why initial HIV transmission, by needlestick injury or by homosexual or heterosexual intercourse with an infected individual, rarely passes on the virus. This infrequency of transmis-

sion is suggestive of a first line of defense that precedes the formation of antibodies. The antioxidant defense system, including the selenoenzyme glutathione peroxidase, seems the most likely candidate for this role. If correct, this hypothesis would explain why HIV/AIDS is most prevalent in low selenium regions of Africa and why it has spread so ineffectively where diets are enriched in this trace element [13,14,22].

Consequences of hypothesis

It has been demonstrated that glutathione peroxidase protects mice against viral-induced myocarditis [29]. Similarly, in humans, selenium appears to reduce Coxsackie B-induced myocardial infarction [30] and infection by Hepatitis B and C [31,32]. If, as suggested here, glutathione peroxidase serum levels play a major role in who is infected by HIV and who is not, the addition of selenium and the amino acids cysteine, glutamine and tryptophan to diets of the poor would provide a further protective strategy against this and other viruses. Such a strategy is desperately needed since HIV continues to spread rapidly around the globe and appears to be on course to fulfill Hasteltine's 1992 prediction that, by 2015, it will have infected a cumulative total of 1 billion individuals [33].

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Nutritional Supplements Can Delay the Progression of AIDS in HIV-Infected Patients: Results from a Double-Blinded, Clinical Trial at Mengo Hospital, Kampala, Uganda

Edith Namulemia, M.BchB., M.Sc. Epid.,[1] James Sparling, M.D.,[2]
Harold D. Foster, Ph.D.[3]

Abstract

Objective: To examine the immunologic, biochemical and clinical effects of two combinations of nutritional supplements on the progression to AIDS of HIV-infected patients not receiving anti-retroviral treatment.

Design: A prospective randomized, double-blinded clinical trial.

Methods: 249 female and 61 male HIV-infected outpatients of Mengo Hospital, Kampala, Uganda, with baseline CD4 cell counts above 200, who were not receiving anti-retroviral drugs, were randomized into Groups A and B. Group A patients received capsules containing 37 nutrients, while those in Group B were given capsules of 30 nutrients. Both nutritional combinations were designed to increase glutathione peroxidase levels. All patients were instructed to take two capsules, three times daily with meals for 52 weeks. 310 patients began the year long study and 263 completed it. The loss to follow-up, therefore, was some 15.2 percent. Serum glutathione peroxidase levels and CD4 cell counts were measured at baseline, after 28 weeks and at the trial's end which was 52 weeks after patients began taking nutrients. Patient weights were recorded at six weekly intervals. Karnofsky scores were used to establish changes in the quality of life and were measured at the beginning of the trial and at 30 and 52 weeks. The study examined the effects of these two combinations of nutrients on biochemical and immunologic parameters, that is, serum glutathione peroxidase levels and CD4 cell counts as the study's primary endpoint. Secondary end points were weight changes and patient assessed quality of life.

Results: The mean/median serum glutathione peroxidase levels in Group A (37 nutrients) increased from 3825/3628 U/L (International Units) at baseline to 8894/8575 U/L at the trial's end ($p<0.000$). Similarly, patients in Group B (30 nutrients) had an increase in mean/median serum glutathione peroxidase levels from 3862/3602 to 9839/9203 U/L over the length of the trial ($p<0.000$). The mean/median CD4 cell counts rose from 400/347 mm^3 to 446/388 in Group A and from 400/335 to 446/394 mm^3 in Group B ($p<0.000$). Mean weight increases over 52 weeks were 1.0 kg in Group A and 1.4 kg in Group B, while Karnofsky scores in Group A rose from 81 to 85 and in Group B from 82 to 86. Wilcoxan Signed Ranks Test and the Sign Test both indicated that all these measured increases within both groups were statistically significant ($p<0.01$). Indeed, for both glutathione peroxidase levels and CD4 cell counts $p<0.000$ in all cases. There were, however, no statistically significant differences between the measured parameters, (serum glutathione peroxidase, CD4 cell counts, weight and Karnofsky scores) in Group A compared with those of Group B ($p>0.05$), or between

1. Principal Investigator, Program Manager AIDS Clinic, Mengo Hospital
2. Internal Medicine and Respiratory Disease, Victoria, BC and Board Member, The Friends of Mengo Hospital (Canada)
3. Professor, Department of Geography, University of Victoria, PO Box 3050, Victoria, BC, Canada. V8W 3P5

Supported in full by the Canadian charity The Friends of Mengo Hospital. Correspondence Address: Harold D. Foster, PhD., Department of Geography, University of Victoria, PO Box 3050, Victoria, BC, Canada. V8W 3P5
email: hfoster@office.geog.uvic.ca

males and females ($p>0.05$).

Conclusions: Specific nutritional supplements, designed to raise patients' glutathione peroxidase levels, appeared to be able to significantly increase CD4 cell count recovery in HIV-infected patients receiving no other medications. This increase in CD4 cell count was associated with an improvement in quality of life and an increase in body weight. The supplements tested were generally well tolerated and appear to hold promise for the prophylaxis of HIV/AIDS. Further nutritional clinical studies appear warranted.

Key Words: HIV, nutritional supplements, selenium, glutathione peroxidase, CD4 cell count, Karnofsky scores

Introduction

There is clearly a relationship between the global diffusion of HIV/AIDS and the nature of local diets.[1] In HIV infection, for example, deficiencies of specific nutrients have been shown to be associated with more frequent opportunistic infections, faster progression of disease and higher AIDS mortality.[2-4] Furthermore, Fawzi and co-workers[5] have reported an increase in CD4 cell count in HIV-infected patients receiving micronutrients.

Selenium appears to play a key role in this relationship. Ogunro and colleagues,[6] for example, have shown that as HIV/AIDS progresses, both plasma selenium levels and mean erythrocyte glutathione peroxidase activity declines. Consequently they suggest that selenium supplementation would be of immense benefit to HIV-1/AIDS infected patients. Kaiser and co-workers[7] also have recently demonstrated that micronutrient supplements, including selenium, N-acetyl cysteine and L-glutamine significantly increased CD4 cell count in HIV-infected patients receiving highly active anti-retroviral therapy (HAART). Indeed, Foster[8] has argued that the major symptoms seen in AIDS are due to extreme deficiencies of selenium and the three amino acids, cysteine, glutamine and tryptophan, caused by production of a homologue of glutathione peroxidase by HIV.

The major objectives of this clinical trial were to establish whether nutritional supplementation could slow the decline of HIV-positive patients to AIDS and improve their CD4 cell counts and quality of life, as shown by Karnofsky scores. If so, the study sought to determine whether such improvements were associated with increases in serum glutathione peroxidase levels.

Method

Study Design

This was a prospective, randomized, double blinded, clinical trial designed to determine the affects of two nutritional supplement mixtures on HIV-1 disease progression, in HIV-infected patients who were not receiving any anti-retroviral treatment. These mixtures were designed to increase the body's production of glutathione peroxidase to determine whether elevated levels of this selenoenzyme changed the natural history of HIV infection.

After the trial had received ethics approval from the Mulago Ethical Review Committee (ERC) and the Uganda National Council of Science and Technology, it was given the International Standardised Randomised Controlled Trial Number 42274642. Before their enrollment, informed consent was obtained from study participants, all of whom were outpatients of the Mengo Hospital in Kampala, Uganda. The trial lasted one year.

Study Subjects and Study Site

Enrollment began in June 2005 and concluded in October of the same year. This individual recruitment process took 2 weeks and so, although patients were involved with the trial for 54 weeks, they actually received the assigned supplements for 52 weeks. By the end of enrollment in October, 310 HIV-positive patients had been recruited. This study size was ad-

equate to bring about a power of 80 percent at a 95 percent confidence interval. 249 of the enrolled patients were female and 61 male. In women, the median age at the trial's start was 36.0 years (25 percentile 30.0 years, 75 percentile 40.0 years). In men, the median age was 39.0 years (25 percentile 33.7 years, 75 percentile 45.5 years). Using a random block design to achieve patient randomization, participants were given one of two nutrient supplement combinations identified as A or B, to be taken three times daily with meals, for 52 weeks (**Table 1,** p.132). Patients who were pregnant, had a baseline CD4T lymphocyte count of 200 or less, or who were receiving anti-retroviral treatment were excluded from trial participation. However, patients who suffered from other additional illnesses, such as tuberculosis, were accepted for enrollment. All clinical staff and student assistants were unaware of the patient group treatment assignments. The labels were attached to all bottles of nutrients by an external co-ordinator in Canada who also kept the code necessary to identify members of the two groups. All trial participants agreed to return, at six weekly intervals, to Mengo Hospital to receive nutritional supplements and for measurement of CD4 cell counts, serum glutathione peroxidase, weight and quality of life assessments as required.

Study Medications

Two nutritional combinations were designed and encapsulated specifically for use in this trial. The medications given to patients in Group B consisted of 30 nutrients with a filler of organic sugar (Table 1). This combination of nutrients had been found, in small open trials, to stimulate appetites in HIV-positive patients[9]. The logic behind this approach was to establish whether greater appetite was sufficient to encourage HIV-positive individuals to increase their consumption of local foods to a point at which enough selenium and amino acids were digested to normalize glutathione peroxidase levels. Serious loss of appetite is a common symptom of HIV/AIDS.[10]

The capsules taken by Group A patients contained the same thirty appetite stimulating supplements, but also included the additional seven nutrients shown in Table 1. The latter nutrients were designed to directly promote the body's production of glutathione peroxidase and, in addition to amino-acid rich desiccated beef liver, included L-selenomethionine, N-acetyl cysteine, L-glutamine, hydroxytryptophan, alpha lipoic acid and ascorbic acid. Patients receiving this mixture of supplements did not have to rely on their own diet to provide the selenium, cysteine, tryptophan and glutamine thought necessary to boost body glutathione peroxidase levels.[11]

Capsule sizes and dosages were identical and their appearances were extremely similar. Both nutrient supplements were taken three times daily (six capsules in total) with food.

Clinical and Laboratory Evaluations

Potential study patients underwent an initial screening at Mengo Hospital. This involved collection of demographic data, medication history and a laboratory testing of CD4T cell levels. Eligible participants then returned to this hospital for baseline and follow-up visits on a six weekly basis for 52 weeks. Glutathione peroxidase levels were measured at baseline on entering the trial, after 30 weeks and at the end of the trial, as were CD4T cell counts. Patients were also weighed during each of their hospital visits. Karnofsky quality of life scores were taken at baseline and at 30 an 52 weeks. Laboratory measurements of serum glutathione peroxidase levels took place at the Mengo Hospital Laboratory, while CD4T cell counts were conducted by the Hematology Laboratory at Mulago Hospital.

Table 1. Nutritional combinations used in Mengo Hospital HIV-Positive Outpatient Trial (Groups A and B).

Amount per Serving (Three servings needed per day)	Group A	Group B
Calcium	23 mg	23 mg
Magnesium	23 mg	23 mg
Boron	0.2 mg	0.2 mg
Zinc	1.1 mg	1.1 mg
Vanadium	2 mcg	2 mcg
Copper	100 mcg	100 mcg
Chromium	8 mcg	8 mcg
Manganese	620 mcg	620 mcg
Silica	770 mcg	770 mcg
AEP Iron (2-amino ethanol phosphate)	600 mcg	600 mcg
Iodine	2.9 mcg	2.9 mcg
Strontium	25.7 mcg	25.7 mcg
Molybdenum	0.3 mcg	0.3 mcg
Vitamin A	390 IU	390 IU
Provitamin A	390 IU	390 IU
Vitamin D_3	31 IU	31 IU
Vitamin B_1	1.9 mg	1.9 mg
Vitamin B_2	1.9 mg	1.9 mg
Vitamin B_3	7.8 mg	7.8 mg
D-Calcium Pantothenate	7.8 mg	7.8 mg
Vitamin B_6	1.9 mg	1.9 mg
Vitamin B_{12}	8 mcg	8 mcg
Vitamin C (calcium ascorbate)	23 mg	23 mg
Vitamin E (D Alpha Tocopheryl Succinate)	5 IU	5 IU
Vitamin K (Phytonadione)	23 mcg	23 mcg
Biotin	8 mcg	8 mcg
Folic Acid	31 mcg	31 mcg
Choline	4 mg	4 mg
Inositol	4 mg	4 mg
P.A.B.A. (Para Amino Benzoic Acid)	2 mg	2 mg
Dessicated Beef Liver (undefatted)	400 mg	Nil
L-Glutamine	180 mg	Nil
Hydroxytryptophan L-5 (5-HTP)	180 mg	Nil
N-Acetyl Cysteine	180 mg	Nil
Alpha Lipoic Acid	30 mg	Nil
Ascorbic Acid	40 mg	Nil
L-Selenomethionine	200 mcg	Nil
Organic sugar as a filler	Nil	Yes

Data and Collection and Statistical Analyses

At Mengo Hospital, patient data was stored in an Access database and data collection forms were created using Access database software. After collection, the data were moved from Access to the statistical package SPSS for analyses.

All statistical analyses were conducted by the Statistical Consulting Centre of the University of Victoria, British Columbia, Canada which recommended the use of Wilcoxan Signed Ranks Tests and the Sign Test to establish the statistical significance of data from baseline to the study's 52 week conclusion.[12]

The study's primary end points were to examine the effects of the two nutrient mixtures on serum glutathione peroxidase levels and on CD4 cell count. Secondary end points were weight changes and general health status as measured by Karnofsky scores. Of particular interest was any delay in the progression of AIDS and the need to start associated anti-retroviral treatment.

Results

310 patients began the trial, 160 of whom were randomly assigned to Group A and 150 to Group B. During its 52 week duration, 47 patients exited the programme, 29 from Group A and 18 from Group B. This represented a loss to follow-up of some 15.2 percent. In Group A, 3 left because of pregnancy, 14 were lost to follow-up, 4 withdrew consent, 2 died from tuberculosis and one from esophageal cancer. Two further patients died from unknown causes and another from severe anemia. In Group B, over the course of the trial, one patient left because of pregnancy, 6 were lost to follow-up, one withdrew consent, four died of tuberculosis, two from cancer and four of undiagnosed illnesses.

As a consequence, 81.9 percent of patients in Group A and 88.0 percent of those from Group B completed the year long trial. The statistical analyses which follow refer to these patients. Beyond simple measures of central tendency, Sign Test and Wilcoxan Signed Rank Tests were used to establish whether the obtained results were statistically significant, at least at the 0.01 level.

Immunological, Biochemical Parameters

From baseline over the one year period of follow up, 92 patients in Group A experienced an increased in the CD4 counts, while the remaining 39 showed a decrease (Table 2, p.134). Nevertheless, the mean/median CD4 count for Group A as a whole rose from 400/347 to 446/388 cells per mm^3. The Wilcoxan Signed Ranks Test and the Sign Test both indicated that these Group A mean/median increases were statistically significant (p=0.000).

Similarly, from base measurement to week 52, 89 patients in Group B showed an increase in their CD4 counts, while the remaining 41 displayed a decrease. The mean/ median CD4 count for Group B, rose from 400/335 to 446/394 over the year. Again the Wilcoxan Signed Ranks Test and Sign Test both established these gains to be of statistical significance (p=0.000).

At the beginning and end of the 52 week trial, glutathione peroxidase levels were measured in 92 patients from Group A. 77 of these patients had experienced an increase in the serum levels of this selenoenzyme, while the remaining 15 showed decreases. As a whole, 92 patients in Group A, for whom serum glutathione peroxidase levels were measured, showed mean/median increases from 3825/3628 U/L at the beginning of the 52 week long trial to 8894/8573 U/L at its end (p=0.000). Similarly, serum glutathione peroxidase levels were measured in 92 members of Group B at the start and endpoint of the trial. 81 of these had experienced an increase and 11 a decrease in serum levels of this selenoenzyme. This group, as a whole, showed rises in mean/median serum glutathione

Table 2. Changes (increases/decreases/no change) in CD4 cell counts, serum glutathione peroxidase, weight and Karnofsky scores from baseline measurement to 52 weeks.

Group A		CD4 cell count	Serum glutathione peroxidase	Weight	Karnofsky scores
	Increase	92	77	69	68
	No Change	0	0	17	27
	Decrease	39	15	41	34
Group B					
	Increase	89	81	76	71
	No Change	0	0	8	27
	Decrease	41	11	42	31

peroxidase levels from 3862/3602 U/L to 9839/9203 U/L over the 52 week trial. Both the Sign Test and Wilcoxan Signed Rank Test established that these increases were of statistically significance (p=0.000)

Clinical Parameters

Over the 52 weeks, 67.7 percent of the patients in Group A either increased, or remained the same in weight. Mean weight increased from 60.1 kg to 61.1 kg. Both the Wilcoxan Signed Rank Test (p=0.001) and the Sign Test (p=0.01) showed this gain to be statistically significant. Similarly, 66.7 percent of the patients in Group B either increased or remained the same in weight over the year long trial. Mean weight for Group B rose from 62.0 kg to 63.4 kg, during the 52 weeks. Again both Wilcoxan Signed Ranks Test (p=0.000) and the Sign Test (p=0.002) demonstrated that weight gain was of statistical significance.

Quality of life, as measured by the Karnofsky scores[13] also had risen during the duration of the trial in both groups. In Group A, for example, these scores rose or remained the same in 73.6 percent of patients, while the mean of this measure increased from 81 to 85 (p=0.000 and p=0.001). In Group B scores rose or remained unchanged in 76.0 percent of patients, while the mean rose from 82 to 86 (p=0.000 in both statistical measures).

Comparison of Groups A and B and of Males and Females

Four Analysis of Variance (ANOVA) models were used to compare changes in CD4 cell counts, serum glutathione peroxidases, weight and Karnofsky scores, over 52 weeks, using two factors; nutritional supplements and gender. Neither of these two factors were significant at the 0.05 level. That is, during this trial, there were no statistically significant gender differences in the results obtained, nor were there any statistically significant differences in changes in CD4 cell count,

serum glutathione peroxidase, weight or Karnofsky scores between Group A and B patients. In summary, both genders showed similar immunologic, biochemical and clinical improvements, regardless of which of the two nutritional combinations they were taking.

Discussion

The major objective of this clinical trial was to determine whether either, or both, of the nutritional supplement mixtures, described in Table 1, could slow or reverse the progression to AIDS of HIV-infected patients who were not taking anti-retroviral drugs. When the trial ended, the majority of patients from both Groups A and B felt that this goal had been achieved. Many patients, for example, described significant appetite increases, together with the return of their ability to walk long distances. Most also reported being happier. The quantitative data supported these claims. It has been long established that selenium and associated glutathione peroxidases are essential components of the human immune system.[14] In the trial described here, two related but distinct, nutritional treatments, were both able to increase serum glutathione peroxidase levels in HIV-infected outpatients by roughly a factor of 2.5, over a 52 week period. Such increases would be very unexpected in HIV-positive patients who are not receiving anti-retroviral drugs since serum selenium and glutathione peroxidase levels both normally decline as HIV/AIDS progresses.[15-16]

Simultaneously, the CD4 cell counts, indicative of an improving immune system, rose in both treatment groups. Such improvements are also atypical of HIV-positive patients not taking anti-retroviral drugs. To illustrate, a healthy CD4 cell count is somewhere between 500 and 1500 cells per cubic millimeter of blood. Normally, as observed at Mengo Hospital and confirmed elsewhere,[17] in HIV-positive patients not receiving anti-retroviral, the count decreases on average about 50 to 100 cells each year. If this is the case, one might have expected CD4 cell counts (mean/median) to have fallen to some 325/272 in patients in Group A and 325/260 in Group B after the completion of the 52 week trial. In fact, these measures of central tendency were, as described, 446/338 and 446/394 at trial's end. That is, both nutrient groups had mean and median CD4 cell counts that were roughly 120 cells per cubic millimeter of blood higher than expected in HIV-positive patients not receiving anti-retroviral treatment. Increases in weight and Karnofsky Score were also indicative of a general clinical improvement in health of both treatment groups. While these relationships do not prove that increasing serum glutathione peroxidase levels cause improvements in CD4 cell counts, weight gains and higher personal evaluation of health they are certainly consistent with this hypothesis. These analyses strongly support providing nutritional supplements for all HIV-1/AIDS patients, although it is clear that further clinical trials are required to establish optimum dosages and nutrient combinations.

Conclusions

This trial shows that both nutrient combinations (Table 1), taken for 52 weeks by HIV-positive patients who were receiving no anti-retroviral drugs, can significantly slow their decline into AIDS. The associated improvement is associated with increases in serum glutathione peroxidase levels, CD4 cell counts, body weights and improvements in quality of life scores. These results are consistent with those of smaller open trials using nutritional supplement which have been conducted elsewhere in Sub-Saharan Africa.[18] It seems clear that inadequate nutrition plays an extremely important role in the progression into AIDS of HIV-infected patients. These results also are consistent with Foster's model[19] of the development

of AIDS which suggests that deficiencies of glutathione peroxidase play a key role in the process.

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